Prodrugs

Medicinal Organic Chemistry
and
Drug Design

By

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المهم التعريف / advantage / المجموعات الداخلة في التكوين

كله مهم

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from inactive to active

Prodrugs (Drug Latentation)

Many drugs have good activity in vitro, but when tested in vivo show weak activities . This was attributed to several factors such as

1.poor absorption(poor solubility)
2.rapid metabolism,(easily oxidized)
3. poor access to the site of action.
4.Unpleasent taste (chloramphenicol,metronidazol, erythromycine.

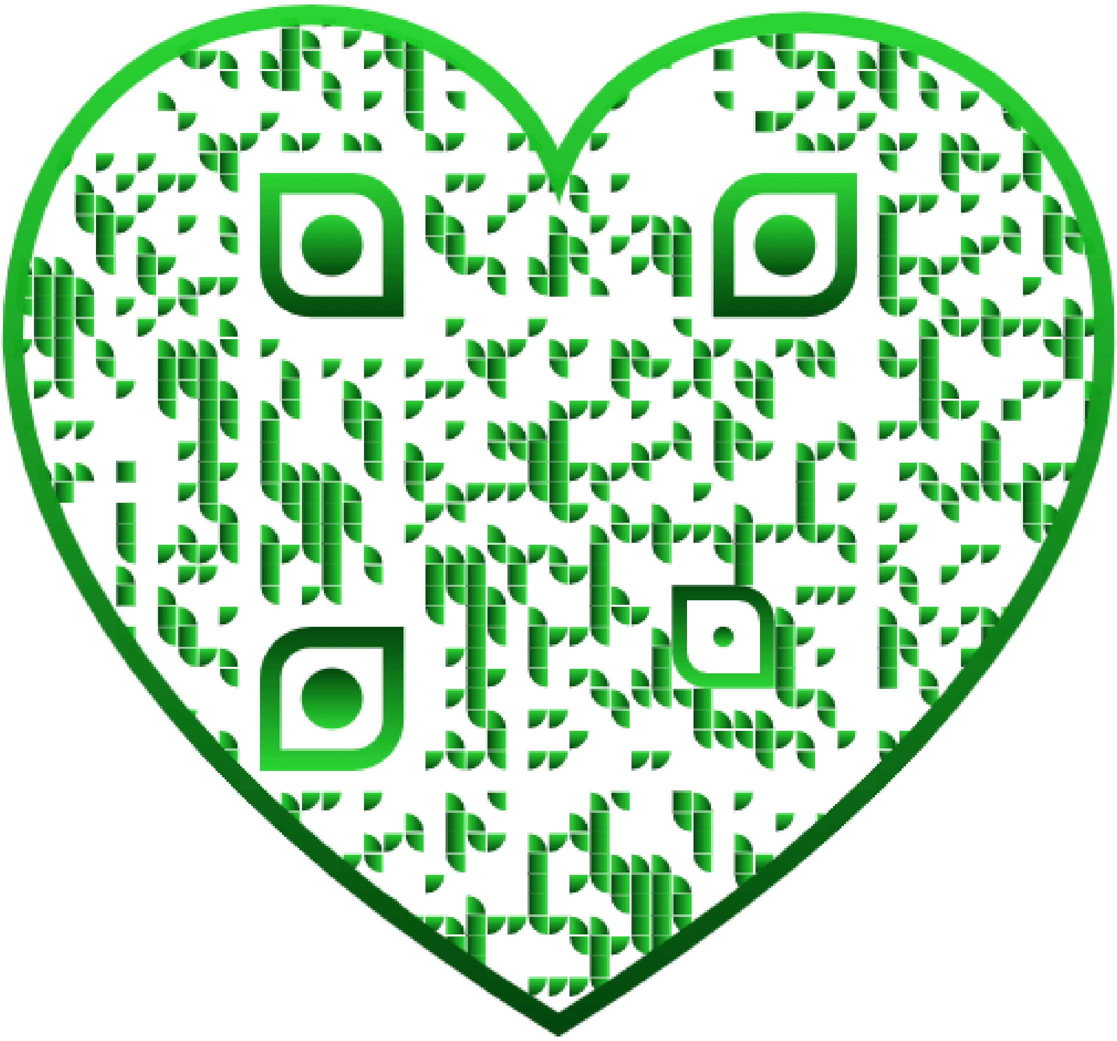
The concept of prodrug was introduced to overcome these problems.

Prodrugs:

Biologically inactive compounds in vitro converted in vivo by enzymatic or non-enzymatic reaction into the active drug.

Prodrugs must be:

1.Well absorbed.
2.Converted to the active drug in the body.
3.Non-toxic regarding groups released from the molecule.

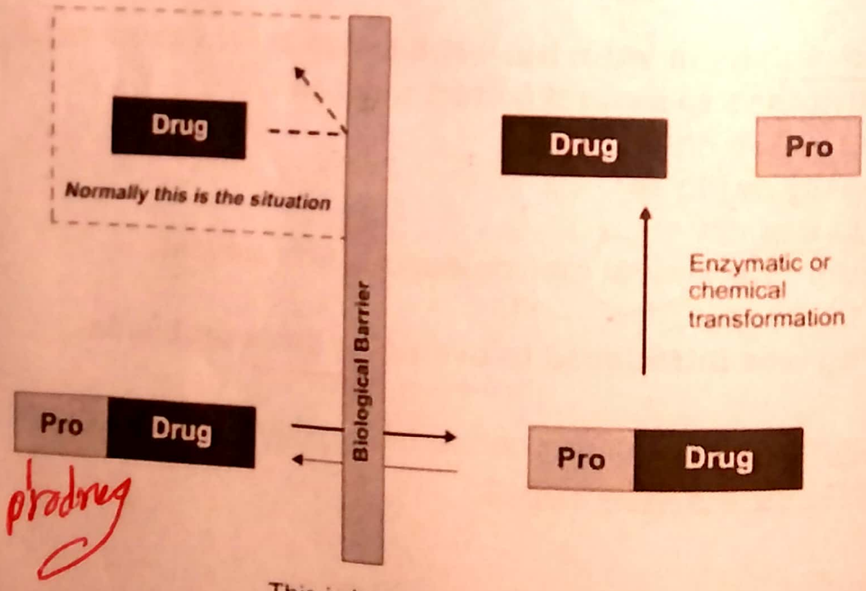


Prodrugs are under taken to improve patient acceptability of the agent(i.e reduce pain associated with administration) alter absorption, alter distribution, alter metabolism, alter elimination.

Advantages of prodrugs

- Increase absorption
- Reduce pain at the site of injection
- Elimination of an unpleasant taste associated with the drug.
- Decrease toxicity
- Decrease metabolic inactivation
- Increase chemical stability.
- Prolonged or shortened action.

يقلل من المفعول او يزود من المفعول


Drug
Normally this is the situation
Biological Barrier
Drug
Pro
Enzymatic or chemical transformation
Pro
Drug
prodrug
Pro
Drug

This is happening in the body.
(*In vivo*)

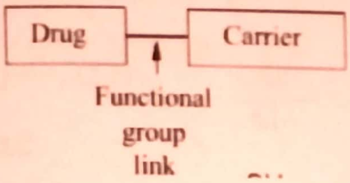
Classification of prodrugs according to functional group

المطوى ح

The groups that are suitable for prodrug synthesis are: $COOH$ OH NH_2

1. Carboxylic acid group for ester and amide
2. Hydroxyl group for ester prodrug
3. Alephatic and aromatic amine for amide
4. Carbonyl compounds containing prodrug.

Functional group
Acids
Alcohols and phenols
Aldehydes and ketones
Amines



اذا شفت مركب فيه أستر قول عليه مباشرة prodrug.

Most common Prodrugs can performed by

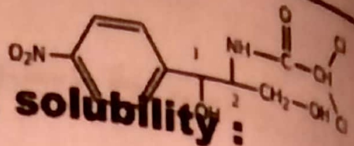
أشهر طريقة لتحضير ال prodrug.

1.Esterfication drug contain alcohol , carboxylic acid as prodrugs :

- Alcohol-containing drugs → acylation with aliphatic or aromatic carboxylic acids to ↓ water solubility [↑ lipophilicity] or with carboxylic acids containing amino or additional carboxylate groups to ↑ water solubility.
- Prodrugs of agents that contain carboxylic acid or alcoholic functionalities can often prepared by conversion to an ESTER.
- This is the most common type of prodrug due to easy hydrolysis of ester giving active drug.

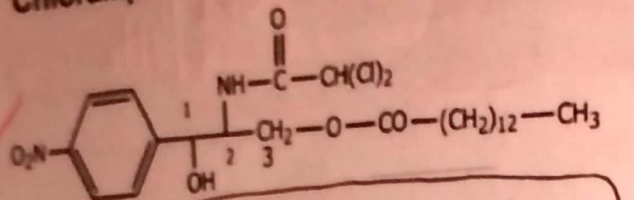
Hydrolysis is done by ESTERASE enzyme present in plasma & tissues .

2.Amide formation with amino group



1. Prodrugs to increase or decrease drug solubility :

Chloramphenicol Palmitate



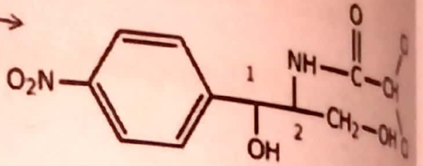
$OH—CO—(CH_2)_{12}—CH_3$

Palmitic acid

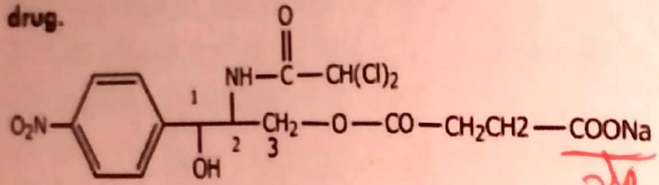
علشان الطعم مر

decrease solubility oral use

To OVERCOME BITTER TASTE
[for pediatric oral suspensions] →
cleaved in duodenum to give active
drug.



Chloramphenicol



ملح

Chloramphenicol succinate

$HOOC—CH_2CH_2—COOH$

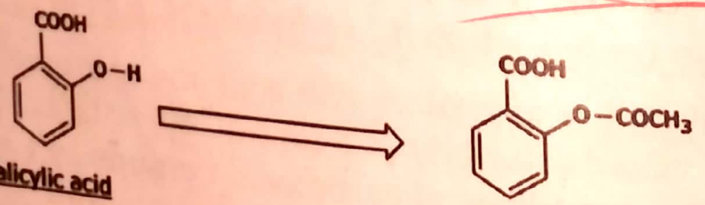
Succinic acid

Increase solubility for IM injection

we use aspirin as prodrug to

2. Prodrugs masking drug toxicity & side effects:

E.g.1:



Salicylic acid

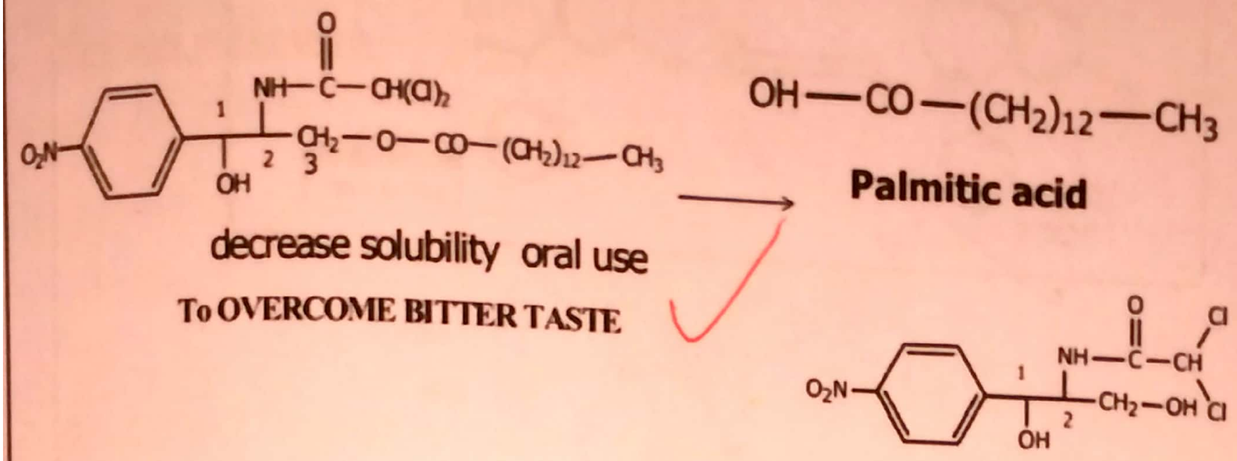
Pain killer but cause gastric irritation & bleeding
[due to its free OH]

Aspirin
[ester prodrug]
hydrolyzed in stomach by esterase enzyme

Amost devoid of gastric ulcer, rapid hydrolysis following absorption

3. Prodrugs to mask bad taste:

E.g. Chloramphenicol [bitter taste antibiotic]
We make *Chloramphenicol Palmitate or succinate* which hydrolyzed quickly after swallowing.
N.B: succinic acid produced on hydrolysis is naturally present in body.



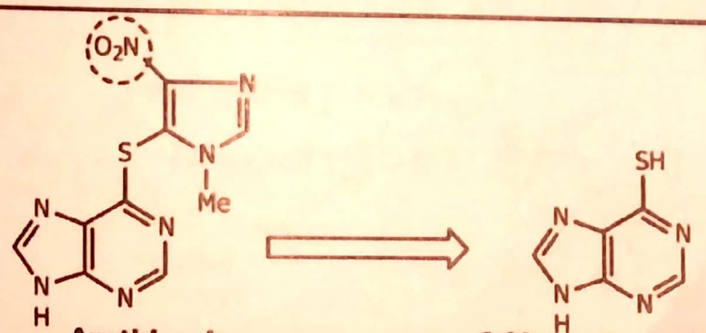
decrease solubility oral use

To OVERCOME BITTER TASTE

4. Prodrugs for prolongation of drug action:

E.g.1:

6-Mercapto purine [short acting] so, → Azathioprine
↑ Electron withdrawing power of the heterocyclic ring → faster release of the active form, so, NO_2 group in Azathioprine ensure a rapid efficient conversion ot 6- mercaptor purine.



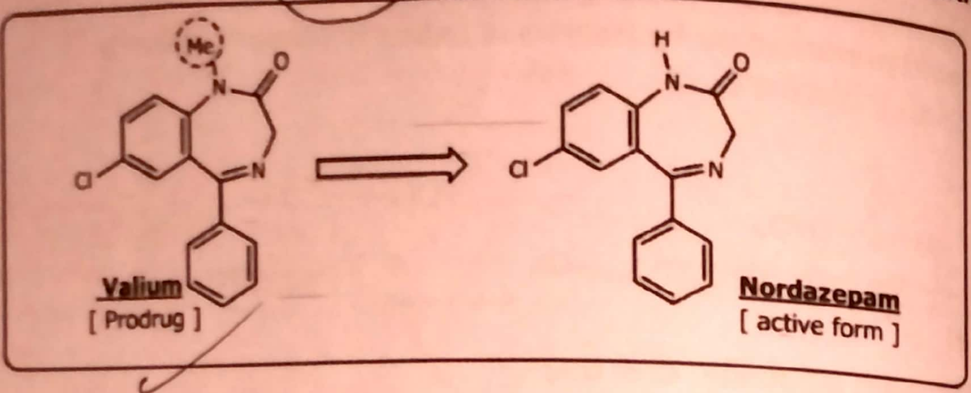
Azathioprine [Prodrug]

6-Mercapto purine [active form]

6-Mercapto purine suppresses the body's immune response and is therefore useful in protecting donor grafts. Unfortunately, the drug tends to be eliminated from the body too quickly.

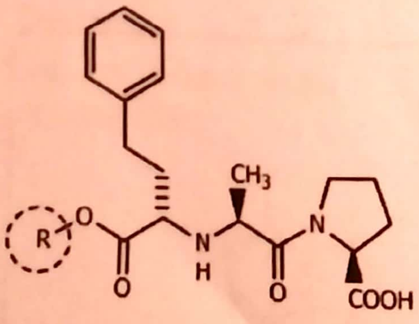
4. Prodrugs for prolongation of drug action:

E.g.3:
Nordazepam [sedative] → Diazepam [Valium®] which is a prodrug → N-demethylation in


Me
N
O
Cl
N
Valium
[Prodrug]
H
N
O
Cl
N
Nordazepam
[active form]

5. Prodrugs to improve membrane permeability

Enalaprilate: with COOH group which is important in binding via ionic or hydrogene bindi of the drug to the receptor BUT *can't cross the fatty layer* so → Enalapril [ester prodrug] which is hydrolyzed in blood stream by esterase enzyme.


R
O
O
N
H
CH_3
O
N
COOH

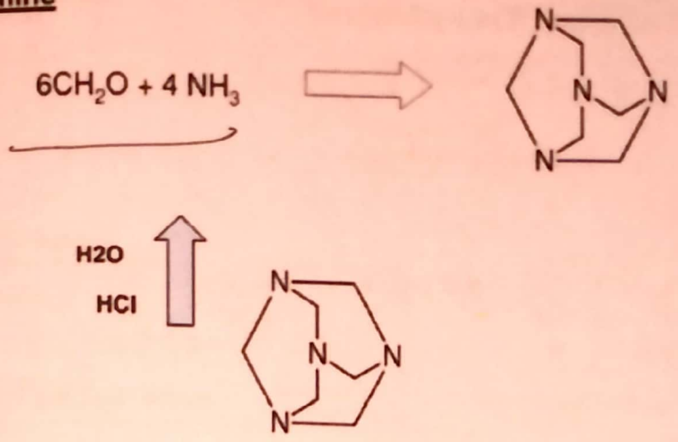
R = H [**Enalaprilate**]

R = Et [**Enalapril**]

6. Prodrugs used in targeting of the drug

Hexamine is a prodrug for formaldehyde used as *urinary tract antiseptic*; it's inactive at pH of the blood [slightly alkaline] so, it passes to urinary tract to be excreted in urine which is acidic due to the bacterial infection → degradation of hexamine to formaldehyde at the site of action.

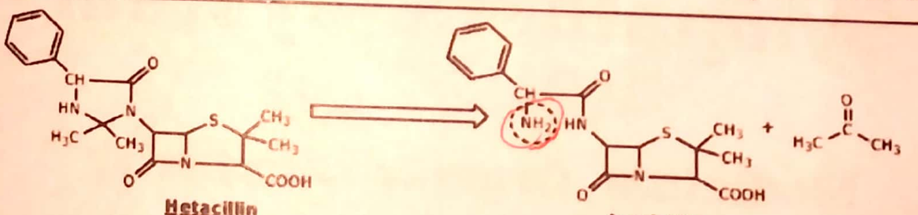
Synthesis of hexamine


$6CH_2O + 4NH_3$
H2O
HCl
N
N
N
N

7.Prodrugs used to ↑ chemical stability:

Intramolecular attack of β-lactam ring by the amino group in the side chain. So, we make:

Hetacillin which is a prodrug of ampicillin prepared to mask the amino group by introducing it into a ring [by acetone introduction] and it slowly releases ampicillin.


CH
HN
N
O
H_3C
CH_3
S
CH_3
CH_3
N
COOH
O
CH
O
NH_2
HN
S
CH_3
CH_3
N
COOH
O
+
O
C
H_3C
CH_3

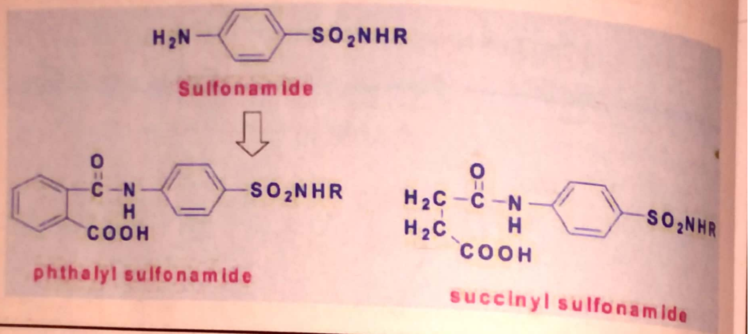
Hetacillin
[Prodrug]

Ampicillin
[active form]

8. Prodrugs used for drug localization:

To increase site specificity of drug in certain site:

Modification of sulfonamide with phathalic or succinic anhydride increases their polaity and subsequent low absorption ,the drug goes down to the lower part of GIT whereby it is hydrolyzed


Sulfonamide
phthalyl sulfonamide
succinyl sulfonamide

Sympathetic System

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[illegible] ©

العمود الفقري المتحكم بالتوصيل والحركة

Symp $\xrightarrow{\text{يطلع من}}$ Thoraco-lumbar.

parasympa $\xrightarrow{\text{يطلع من}}$ Sacral outflow
cranio → 3 9 10 → 4

اذا صار اختلاف imblance b/w sympa or para هنا يبدأ تصرف الدواء
(نقص الزايد وازيد الناقص.)

ganglia ← توصيل (عبارة عن محطات) لسيال العصبي تدفعه من جسد ال pulse
تعمل impluum تكبير لل puls

Somatic ← لا يوجد عنده ganglia

في حالة ال sympa ~~[illegible]~~ ← لما يكون ال ganglia قريب العمود الفقري بيكون pre
ما قبل ال ganglia ← short ← pre
ما بعد ____ ← Long ← post

في ال Para ال pre تكون طويل long
ال post تكون short

المتحكم في GIT para

في ال para ناقل واحد Ach
في sympa ناقلين Nor, adr

يفرز ال Nor (الشق) ← من presynaptic يخرج من الحويصلات
كمية كبيرة adr ← من modular يخرج الى الدم ويتوزع الى بقية الانسجة.
preganglion ← خروج النواقل من نهاية العصب ودخول الاعضاء ويؤدي الوظيفة
اذا الشي ارفع ال Nor اوقف حقة الميتوبلازم.

ال para في القلب قليلة المتحكم في القلب اكثر sympa
مثلا اذا زودت الجرعة حق ال para راح يشتغل على القلب لكن في الجرعات العادية لا مستقبلات ال Muscarinic في القلب قليلة.

post في العضو
pre في العصب

RAF

في ال **para** بالنسبة للقلب ← M_2

بينما M_1 و M_3 موزعة على بقية الجسم بشكل عام لما نجي الدواء راح يشتغل على أغلب المستقبلات لأنه لا توجد أدوية متخصصة على المستقبلات وأكبر دليل دواء الاتروبين والاعراض الجانبية له. ولذلك تم تقسيمها هكذا.

← بينما ادوية ال Sympa متخصصة على المستقبلات α ، β

بالنسبة لمستقبلات ال Sympa كلهن postsynaptic ماعدا α_2 ← **presynaptic**

α_1	α_2	B_1	B_2
→ postsynaptic → main artery , vein (V.C) → eye → mydriasis → α_1 → in sphincter (V.C) تعمل حبس للبول والبراز → blood vessels for hair الشعر	presynaptic (قبل الفصول في العصب) in CNS عملها عكس لما تنشط تقوم تمنع خروج NOR وبالتالي الضغط يقل	post → Heart → coronary artery → kidney	post Bronchia smooth muscle of blood vessels اي يتوجد في كل ال smooth muscle سوى كان اوعية دموية او القصبات الا في العين B_2 ← smooth M of eye
uses → α_1 agonist تستخدم لرفع الضغط في حالة الهبوط hypotension (moderate) تزيل الاحتقان في حالة الاحتقان Nasal decongestion	α_1 agonist تستخدم لخفض الضغط لماذا؟ لان موقعها فوق المتحكم هي agonist لكن عملها antagonist	uses تستخدم في حالة Bradycardia	B.D
α_1 agonist مع ادوية السعال الجاف // // مع ادوية الاحتقان الانف moderate hypoten مع ادوية // // //	تستخدم α_2-agonist في حالة ضغط الحوامل العالي الدواء الذي يخفض ضغط الحوامل ← α_2-agonist α-methyl Dopa		B_3 post in liver, pancrease ↑ Glucose
اذا كان ضغط المريض sever نعطي adr مع اتروبين			

ال sphincter حق اللعاب تنغلق بواسطة α_1 وبالتالي تكون viscous لزج

α_1 في الكلى بتزود دخول الدم الى الكلى V.C

B_2 في الرحم تعمل smooth muscle relax لذلك تأتي مع بعض الادوية وبالتالي تكون مناسبة للحفاظ على الجنين من الاجهاض

RAF

Triemer ← رعشة نتيجة زيادة الدم في الاطراف (الرعشة بسبب اهتزاز العصب)

سخونة في الاطراف تلاحظ في بعض كبار السن

Claudication ← نتيجة نقص الدم في الاطراف وهذا عرض جانبي من

اعراض ال propranolol NON-selective β-blocker (برودة في الاطراف)

myelan-sheath عبارة عن يغطي الخلية العصبية اذا حدث تسرب للشحنات (شحنات كهربائية)

يحدث للشخص تنميل في الاطراف لذلك نعطي المريض فيتامين B_{12} , B_6

كل النواقل الكيميائية في ال Sympa ادرينالين ونورادرينالين ما عدا sweat gland //

adrenal medulla الناقل معهم استيل كولين Ach

من اجل الشخص يتعرق السلك Sympa والناقل او الموصل para

في حالة الجنس اشتغل Sympa و para

سبحان الله في العين } في العين ال para يعمل انقباض ← تنحية العضلات

ول Sympa // //

Sympa يشتغل على العضلة الطولية radial mucle ← انقباض .

ال para يشتغل على العضلة الدائرية circular muscle ← انقباض .

مستقبل B اكبر من مستقبل α بسبب زيادة الكربونات في B

Nor $\alpha \overset{\text{اكبر}}{>} B$

adr $\boxed{B} > \alpha$

قوة يشتغل على القلب لذلك اذا الشخص عنده هبوط شديد في الضغط الافضل نعطي له ادرينالين وليس Nor لان الادرينالين اشتغال قوي على B_1 في القلب

اذا اردت ان تحضر او تصمم α pare ماذا تعمل؟

مثلا اذا قلت ينقص كربونات ينقص الطول

واذا شلت كربونات كثير يضعف الدوار

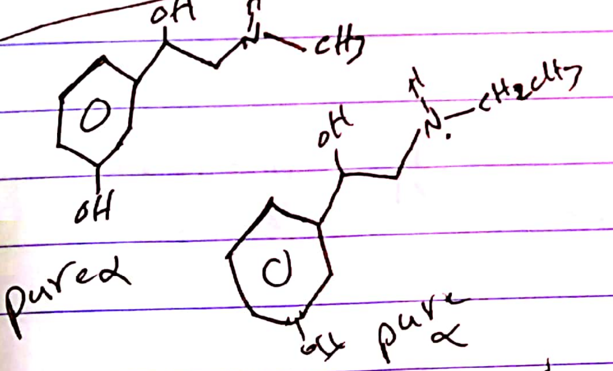
اذا اردت α صافي نقص OH

نشيل para-OH لان الالفة حق OH عالية

الحد المسموح لك كربونتين .

فاذا زيدت كربونه صار كربونتين عادي

CH_2-CH_3 ما راح تؤثر لماذا لان السالبية حق OH عالية فلما شلت OH صغر الدوار



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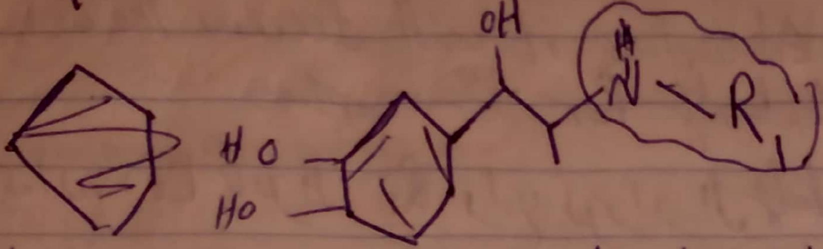
← كلما تزداد عدد ذرات الكاربون التي بين ال amino و ال ring هذا يؤدي ل
decrease the adrenergic activity

① R_1 substitution on amino nitrogen. ①



Nitroge atom, play important role in determination of adrenergic activity, and the replacing of N with C result in a large decline in adrenergic activity and the activity also affected by the no of subsitiution on nitrogen atom.

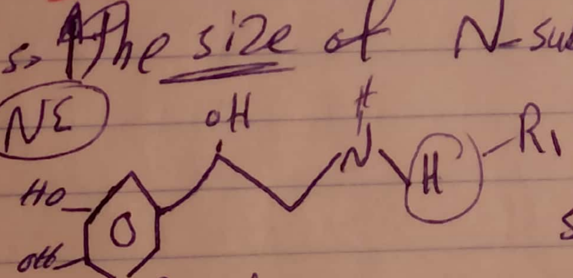
اذاً أن وجود ذرة ال N_1 حيزيد من adrenergic activity بينما لو استبدلت بذرة كاربون راح تقل ال activity

وبالنسبة لل R_1 هي المجموعة المعوضة المرتبطة بال N نوعها وحجمها هما راح يأثرو على (activity) وعلى selectivity.
adrenergic drug

كلما زاد حجم ال R_1 من H الى CH_3 هنا راح يزيد ال selectivity towards B-receptor.

→ So ↑ the size of N-substituents → ↑ B-activity ↓ α-activity

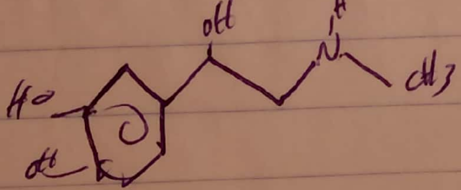
① (NE)



has no B action

So has more α-activity than B
لأن $R_1 = H$

② E



potent agonist at α and B receptor
لأن ال $R_1 = CH_3$
↳ increase B-activity

E- is more B than NE

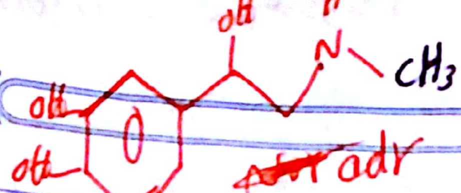
Ⓑ receptor has [larger lipophilic binding pocket

① ↑ size of R_1 → ↓ activity for adrenergic → ↑ selectivity for B-receptor

- when we add CH_3 to Adrenaline it will decreas The activity and incerase selectivity for B-receptor.

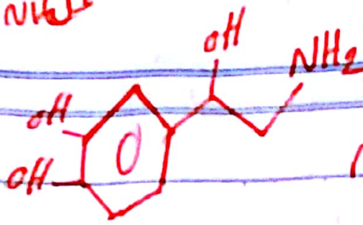
إذا إنه كلما يكبر ال R_1 راح تزداد ال selectivity لل B-receptor

ايضا لانه كلما يكبر ال R_1 راح تزداد ال lipophilicity


OH
H
N
CH3
OH
OH

adr

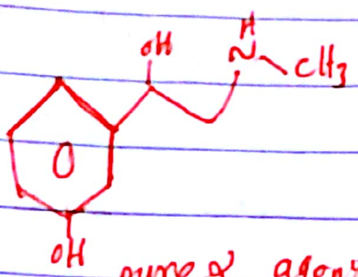
ديمة صغير ماهيش استبدال
على NH2



Nor

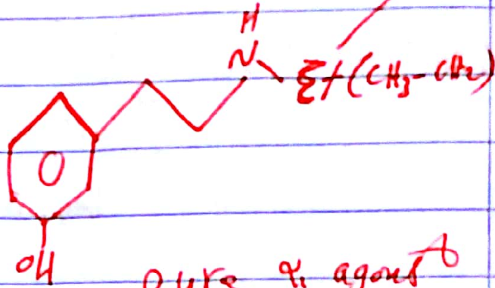
mixed B, α agonist NON seletive
but β > α

α > β



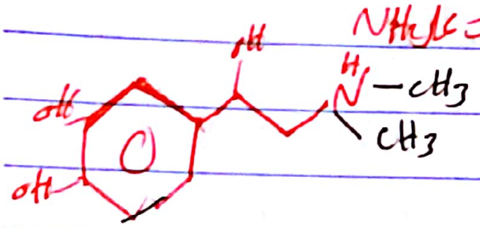
pure α1 agonist

مجموعة ايثيل


H
N
Et (CH3-CH2)
OH

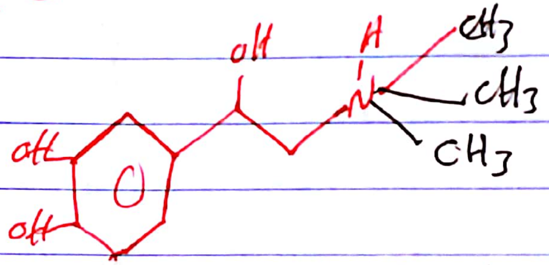
pure α1 agonist

تعميم B زود كربونات = على NH2


OH
H
N
CH3
CH3
OH
OH

B1 B2-NON selective

له action عليهم الاثنين

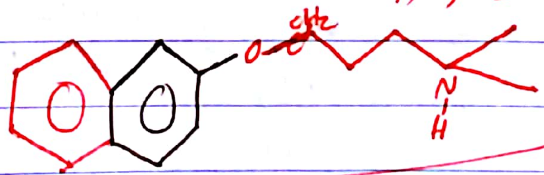

OH
H
N
CH3
CH3
CH3
OH
OH

B2-agonist seletive

لما زودت كربونات زادت selectivity باتجاه B2

قواعد B-Antiagonist

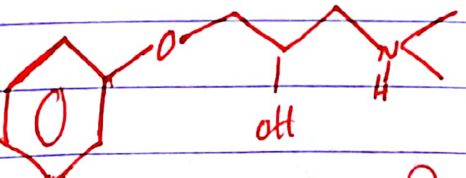
اذا وجدت حلقة بجور حلقة البنزين وبينهما O-CH2 - يعتبر المركب
B-antiagonist NON-seletive
يشتغل على B1, B2, B3



تعمل B1-Antiagonist seletive

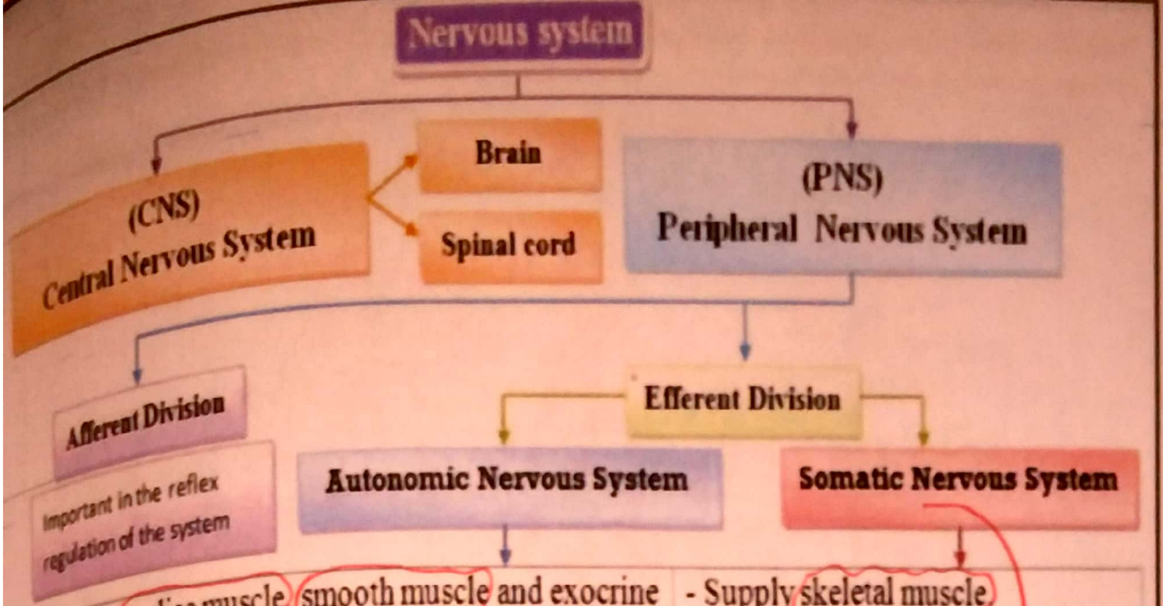
O ← CH2 + حلقة واحدة فقط

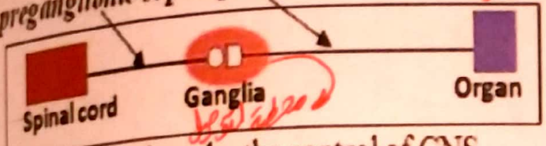
لو جات
تفرعات
حلقات
ع
ليبوفيلية
او OH



selective B1-antagonist

RAF


Nervous system
(CNS)
Central Nervous System
Brain
Spinal cord
(PNS)
Peripheral Nervous System
Afferent Division
Important in the reflex regulation of the system
Efferent Division
Autonomic Nervous System
Somatic Nervous System

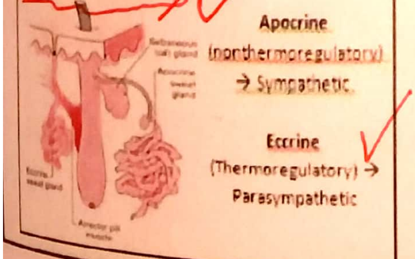
- Supply cardiac muscle, smooth muscle and exocrine gland. - ***Relay*** in autonomic ganglia which consist of ***preganglionic*** & ***postganglionic*** fibers. [illegible]  - ***Involuntary*** → under the control of CNS.	- Supply skeletal muscle. - ***Don't relay*** in ganglia. ✓ ganglia somatic لا يوجد - ***Voluntary***. ✓

Spinal cord
Ganglia
Organ

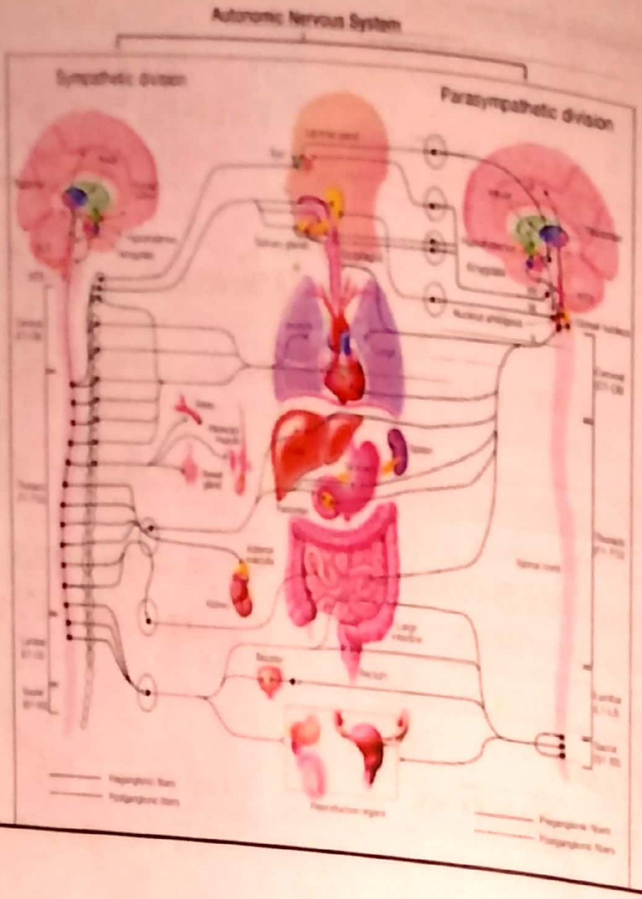
GIT

[illegible] (GIT) [illegible]

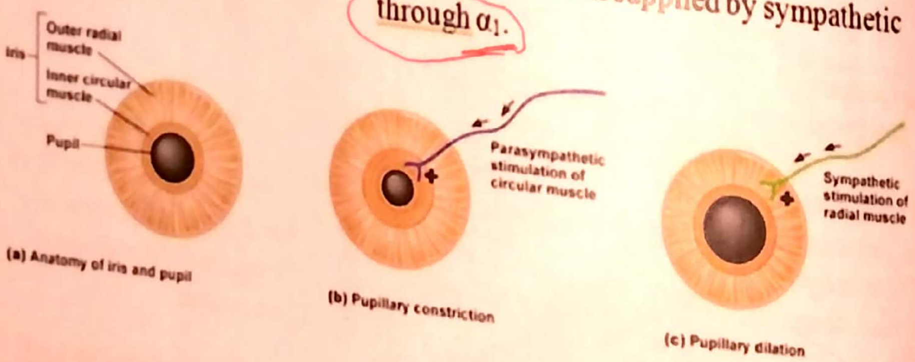
sympa
para

1) Sympathetic	2) Parasympathetic	3) Enteric neurons
(Thoraco-lumbar outflow) → Arise from thoracic and Lumbar regions (L_1 to L_2) of the spinal cord. فردي زوجي	**(Cranio-sacral outflow)** → Arise from cranial nerves 3rd (Oculomotor) 7th (Facial) 9th (Glossopharyngeal) 10th (Vagus) and from 2nd, 3rd and 4th sacral segments.	- The enteric nervous system is the ***third division*** of the ANS. - It is a collection of nerve fibers that innervate GIT. - This system functions independently of the CNS and control the motility, exocrine and endocrine secretions. - It is modulated by both the sympathetic and parasympathetic nervous system.
- Consist of ***short*** preganglionic fibers and ***long*** postganglionic fibers.	- Consist of ***long*** preganglionic fibers and ***short*** postganglionic fibers.	
Chemical transmitters - Adrenaline and Nor-adrenaline → **Except at**- Thermoregulatory sweat gland and adrenal medulla they release Ach ✓  Apocrine (nonthermoregulatory) → Sympathetic Eccrine (Thermoregulatory) → Parasympathetic ✓	Chemical transmitters - Ach (Acetylcholine) 	

- Most organs are supplied with dual innervations of sympathetic and parasympathetic which produce opposite effect.


Autonomic Nervous System
Sympathetic division
Parasympathetic division
Preganglionic fibers
Postganglionic fibers
Reproductive organs

- **Some organs are Supplied with one division of ANS :-**
  - Constrictor pupil (circular) muscle → Cause miosis supplied by parasympathetic through M_3.
  - Dilator pupil (radial) muscle → Cause mydriasis supplied by sympathetic through α_1.
  - Erector pale muscle of skin → Cause hair erection supplied by sympathetic through α_1.


Iris
Outer radial muscle
Inner circular muscle
Pupil
Parasympathetic stimulation of circular muscle
Sympathetic stimulation of radial muscle

(a) Anatomy of iris and pupil

(b) Pupillary constriction

(c) Pupillary dilation

Autonomic receptors

Parasympathetic (Cholinergic receptors)

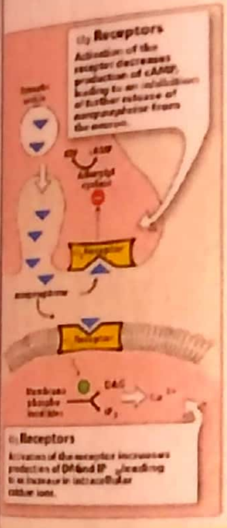
- Peripheral Cholinergic (Muscarinic receptors)
  - Stimulated by muscarine
- Central Cholinergic (Nicotinic receptors)
  - Stimulated by low conc. of nicotine

Sympathetic (Adrenergic receptors)

← كل فردي انقباض α_1 β_1
← وكل زوجي انبساط α_2 β_2
لكن فيه شواذ

Sympathetic (Adrenergic receptors)

α (Alpha adrenergic receptor)



α subdivision

- α_{1A}, α_{1B}, α_{1C} & α_{1D}
- α_{2A}, α_{2B} & α_{2C}

For example →
Tamsulosin is selective α_{1A} antagonist.

α_1 (excitatory) G_q
- *Postsynaptic* on effector organ e.g **Eye and Vascular smooth muscle.**

Action
↑
VC
Mydriasis

α_2 (Inhibitory) G_i
- *Presynaptic* nerve ending
- β cell of pancreas

Action
↓
CNS most
Symp. activity
Renin and insulin
Nor-Adrenaline
(Feedback inhibition)

β (Beta adrenergic receptor)

β_1 (excitatory) G_s
Heart
kidney
CNS
Postsynaptic effectors cells especially →
Heart

Action
↑
Renin
Heart contraction
lipolysis

β_2 (Inhibitory) G_i
- Postsynaptic effectors cells especially →
Bronchi, GIT and Skeletal muscle of blood vessels

Action
VD, Bronchodilatation,
Relax smooth muscle (Uterine) and skeletal muscle twitches (VD)

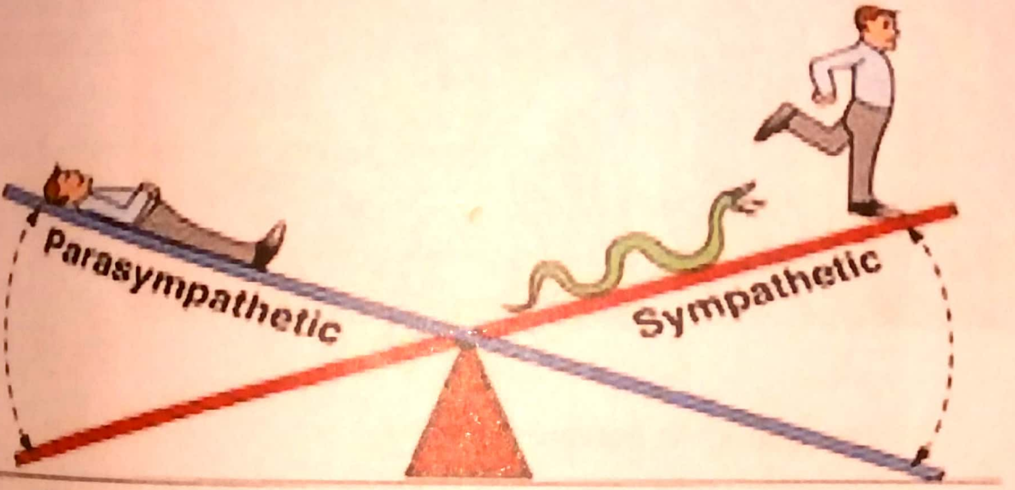
- in liver
β_3 (excitatory) G_s
- increase lipolysis (increase FFA)

Effect of stimulation of Sympathetic and parasympathetic

Organ	Receptor	Parasympathetic	Receptor	Sympathetic
Eye 	M_3	Contraction circular muscle → Miosis	α_1	Contraction radial muscle → Mydriasis
Heart 	M_2	Decrease cardiac properties (-ve) Inotropic (-ve) Chronotropic (-ve) Dromotropic	β_1	Increase cardiac properties (+ve) Inotropic (+ve) Chronotropic (+ve) Dromotropic
Bronchi 	M_3	- Bronchoconstriction - ↑ Secretion	β_2	- Bronchodilatation - ↓ Secretion
GIT 	M_3	- Contraction of wall - Relaxation of sphincters	α & β	- Relaxation of wall (β_2 & α_2) - Contraction of sphincters (α_1)
UB 	M_3	- Contraction of wall. - Relaxation of sphincters.	α & β	- Relaxation of wall (β_2) - Contraction of sphincters (α_1)
Uterus 	M_3	- Contraction	β_2	- Relaxation
Salivation 	M	- Increase (Watery)	α_1	- Decrease
BV 	M_3	- Vasodilatation (VD) → due to release of NO	α & β	- Vasoconstriction (VC) → α_1 - Vasodilatation (VD) on Skeletal muscle → β_2
Sex organ 	M_3	- Erection	α_1	- Ejaculation
Insulin release	M	- Increase	α & β	- Increase → β_2 - Decrease → α_2 (Main effect)
Metabolism	- Increase lipolysis → β_3 - Decrease lipolysis → α_2 - Increase Renin release → β_1			- Gluconeogenesis → β_2 & α - Glycogenolysis → β_2 & α - Decrease Renin release → α_2

- Inotropic → Force of contraction.
- Chronotropic → Heart rate.
- Dromotropic → Conduction of the electrical impulses in the heart
- Bradycardia → Heart slowness
- Tachycardia → Accelerated of the heart

	Parasympathetic	Sympathetic
Actions	Usually antagonist but both increase atrial conductivity and salivaton	
a-type	Usually localized	Usaully Generalized
b-Aim	Conserved energy	Stress(fight &fright
c-pupil	Constricted(Miosis)	Dilated(mydriasis)
d-salivation	watery	viscid
e-bronchi	Constricted	Broncho-dilation → β_2 → agonist
f-heart	↓ All properties but ↑Atrial conductivity (-) (-) (-)	↑ All properties (+) inotropic (+) chronotropic (+) dromotropic
g-Blood pressure	hypotension	hypertension
[illegible] h-GIT مرونة [illegible] الملساء	↑ wall ↓ sphincter lead to Defecation	↓ wall, ↑ sphincter
i-urinary bladder	↑ Wall ↓ sphincter lead to urination	relax Smooth ↓ Wall, ↑ sphincter تقفل
J-sex organ	erection	ejaculation



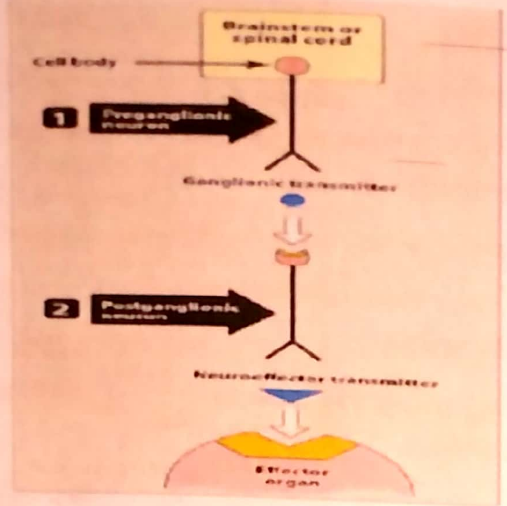
Rest-and-digest: Parasympathetic activity dominates.

Fight-or-flight: Sympathetic activity dominates.

Efferent neurons

The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons

The first nerve cell is called a preganglionic neuron, and its cell body is located within the CNS. Preganglionic neurons emerge from the brain stem or spinal cord and make a synaptic connection in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system).
These ganglia function as relay stations between a preganglionic neuron and a second nerve cell, the postganglionic neuron.


Brainstem or spinal cord
Cell body
1 Preganglionic neuron
Ganglionic transmitter
2 Postganglionic neuron
Neuroeffector transmitter
Effector organ

THE Simpsons

The Autonomic nervous system

Sympathetic activation

Increase BP, heart rate, aggressiveness
Transmitters: Adrenaline/ noradrenaline

Parasympathetic activation

Decrease in BP, heart rate, calmness
Transmitter: acetylcholine

مستقبل B | أكبر من α

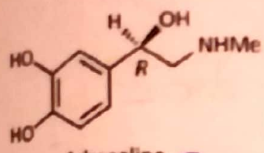
Peripheral nervous system

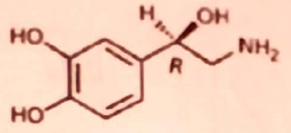
Acetylcholine is the crucial neurotransmitter in the cholinergic system

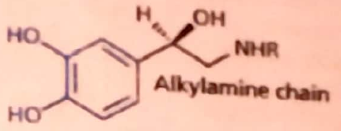
The adrenergic system, which makes use of the chemical messengers adrenaline and noradrenaline.

Noradrenaline (also called norepinephrine) is the neurotransmitter released by the sympathetic nerves, which feed smooth muscle and cardiac muscle, whereas adrenaline (epinephrine) is a hormone released along with noradrenaline from the adrenal medulla, and circulates in the blood supply in order to reach adrenergic receptors.

The action of noradrenaline at various tissues is the opposite to that of acetylcholine, which means that tissues are under a dual control. For example, if noradrenaline has a stimulant activity at a specific tissue, acetylcholine has an inhibitory activity at that same tissue.

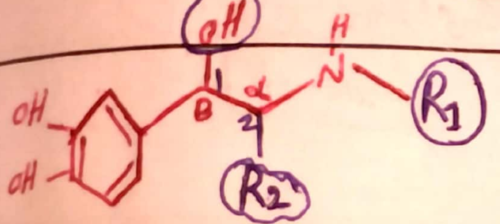

Adrenaline

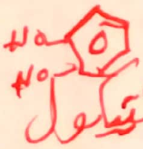

Noradrenaline



Catechol ring system

او [illegible]





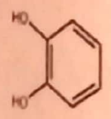
كلهم معاهم حلقة كتيكول
- Nor
- adr
- Dopa
- Ser

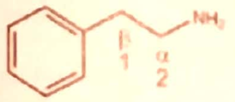
Sympathomimetic agents

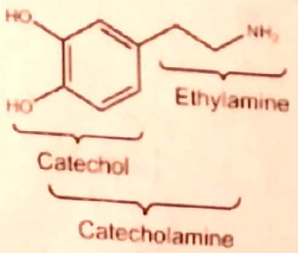
It may be
1. Directly acting: interact directly with the receptor e.g E & NE
2. Indirectly acting: cause release of NE from nerve terminals
3. Mixed.

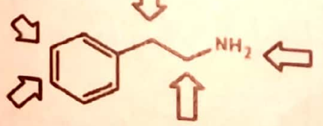
All are β-phenyl-ethamolamine derivatives

·Type of substitution determine: type of activity, mechanism of action & selectivity.









Receptor	α_1	α_2	β_1	β_2
Effectively Binds	Epinephrine (E) & Nor-epinephrine (NE)			E

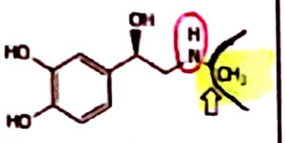
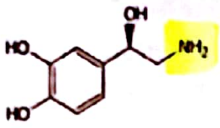
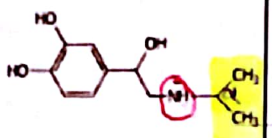
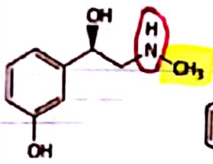
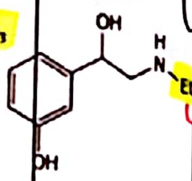
B>α

α>β

✓ ✓

* ركز على عدد ذرات الكربون المتصلات بـ NH

* كلما تزداد ال size of R_1 ← راح تقل ال activity وتزداد selectivity for B receptor.

Adrenaline (E)	Noradrenaline (NE)	Isoprotrenol	Phenylephrine	Etilefrine (Effortil®)
 Larger substituents on this nitrogen shift selectivity toward beta receptors		 B_1, B_2 PROTOTYPE		ر  أشالها وبنزال α CH_3-CH_2
$B > \alpha$ α & β agonist (mixed)		Pure β-agonist	α_1 Pure α-agonist	Pure α-agonist
Uses: 1.Treatment of severe hypotension. 2.Locally to stop bleeding. 3.Smooth muscle relaxation		Non-selective action on B_1 and B_2 Bronchodilator asthma	uses moderate hypoten Nasal decongestant drop رو قطر	Treatment of mild hypotension while Adrenaline used in severe hypotension

في حالة الاسنان

إذا تريد α صافي تقص OH

تشيل para-OH

موجود ✓

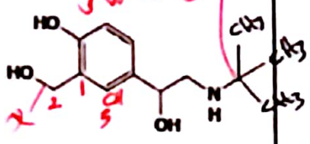
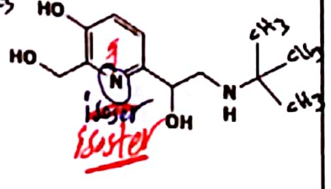
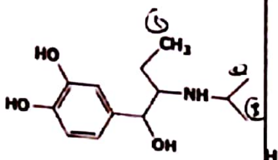
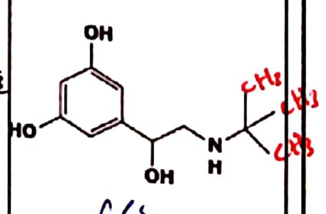
الأهم

$B_2 > B_1$

غير موجود

غير موجود في السوق

موجود ✓

Salbutamol (Ventolin®)	Pributerol	Isoetharine	Terbutaline
الشق الأساسي 	 isoster		 $B_2 > \alpha_1, \alpha_2$
Short acting 2-tert-butylamino-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol	**less muscle tremors**		
	Used for treatment of the asthma		

and cough السعال

علاج Asthma

من الآثار الجانبية إذا زادت الجرعة قد يرفع ضربات القلب reflex Tacycardia

Adrenergic binding site.

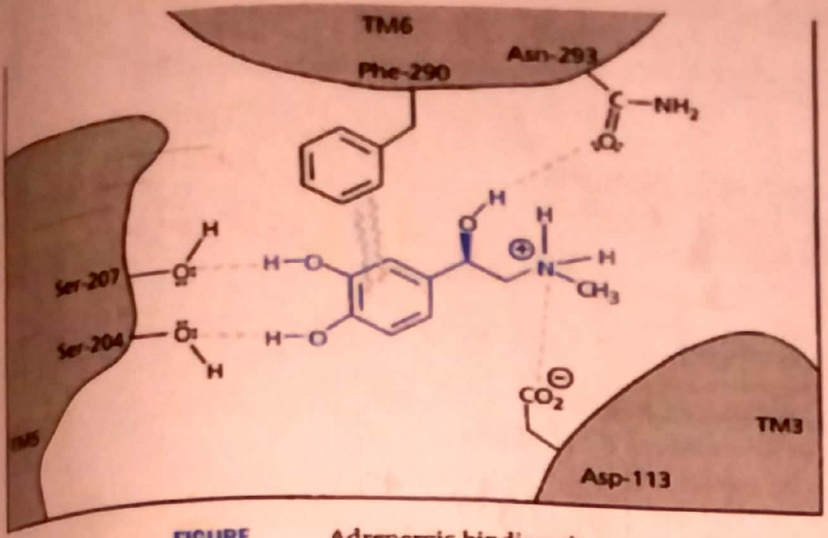
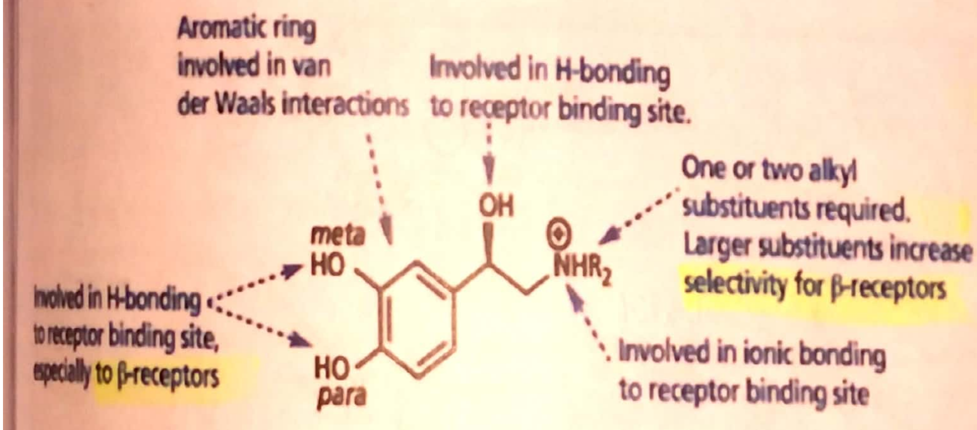

TM6
Phe-290
Asn-293
C—NH₂
O
H
O
H
N
CH₃
Ser-207
O
H
H—O
Ser-204
O
H
H—O
CO₂
TM3
TM5
Asp-113

FIGURE Adrenergic binding site.

علاقة الشكل بالفعالية

Structure-activity relationships → SAR


OH
meta
HO
NHR₂
HO
para

Aromatic ring involved in van der Waals interactions

Involved in H-bonding to receptor binding site.

One or two alkyl substituents required. Larger substituents increase selectivity for β-receptors

Involved in H-bonding to receptor binding site, especially to β-receptors

Involved in ionic bonding to receptor binding site

FIGURE Important binding groups.

بكل زوجين انبساط.

β_2 Agonists and the treatment of asthma

Adrenaline non selective interacting with all adrenergic receptors

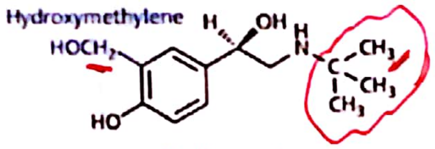
Isoprenaline nonselective interacting with all β subtypes receptors

α2 antagonist → فعلها ترفع الضغط

α2-Agonist → تعمل تنقص الضغط

Salbutamol selective β_2 Agonists

زودت كربونات للـ Branch قلت الـ activity على الـ B1 وزادت الـ selectivity على الـ B2



R-Salbutamol

Selective β_2 agonists. → treat asthma

← دواء الـ Salbutamol له action ضعيف على B1 في بعض الأحيان إذا زادت جرعته ضربات القلب ترتفع قليل وهذا يعمل reflex tachycardia

---

α1 معظم أدوية الزكام فيها بينما أدوية السعال فيها B2 تعمل توسيع

وكذلك B2 أدوية Asthma

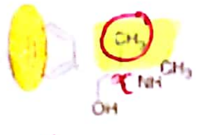
احمرار العين نتيجة V.D لتحسس دواء V.C

Direct and indirect acting sympathomimetics

→ Indirect acting because [illegible] NON CAS

α

no catechol ... good CNS penetration, reasonable duration of action

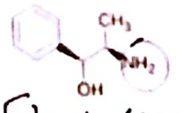


Ephedrine

Indirect معظم ان خاصة النيوتين لا يوجد فيها OH

uses decongestion

no methyl ... no beta 2 agonism

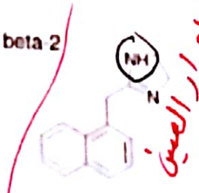


كان قديما اسمه (سكوالنيد)

Phenylpropanolamine

(Propardine)

α يشتغل يرفع الضغط بقوة لذلك يعمل stroke في الدماغ لذلك سحب من السوق



Naphazoline

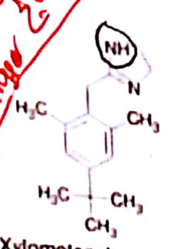
(Presoline)

2-(1-naphthylmethyl)-2-imidazoline

يرغم من شكله ولكن ما زال شغال على α

صعوبة عن الدراسات ادامه ب NH و حلقة تأثير عالي وشغال α

يعالج احمرار العين ويعالج mildhyper



Xylometazoline

(Otrivin)

يرغم من معكله لكن ما زال شغال α

Adrenergic receptor antagonists

in congestion heart failure.

رفع الضغط

General α2, β1-blockers

Carvedilol and labetalol are agents which act as antagonists at both the a- and P-adrenoceptors. They have both been used as antihypertensives, and carvedilol has been used to treat cardiac failure.

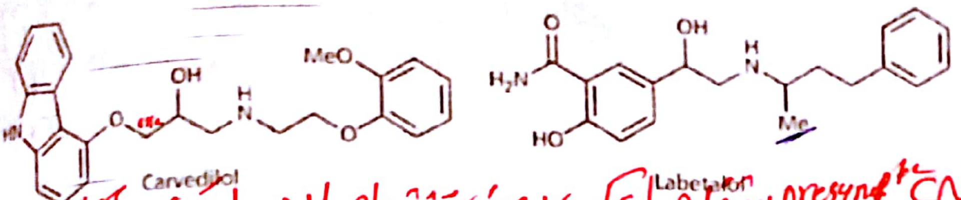


FIGURE 23.21 General α/β blockers.

α2 يتوجد في CNS presynaptic عكس بعض تنشيطها يعمل قفل للـ receptor المسؤول عن تحرير Nor و Dopa، و Ser تعمل hypotension والقلق والاكتئاب بشدة لعدم تحرير النواقل العصبية.

خلاص انت لما تجيب α2-Block راح تقفلها و [illegible] بيدوا حتعمل تحرير للنواقل العصبية وبالتالي تعالج الاكتئاب.

α1-block ادوية قليلة في السوق لأن لها عيوب كثيرة

في الحالة الطبيعية عندما تنشطها Agonist تعمل V.C ـ ترفع الضغط تعالج الهبوط

لما تقفلها بدواء α1-antagonist راح تعمل ←

① sever hypotension

② Na-water retension

severe hypo فيعمل reflex tachycardia ـ اي انه لما تتوسع الشرايين نتيجة α1-block يقوم القلب يحاول يعوض النقص الذي بيحدث وبالتالي تزيد ضربات القلب ويؤدي الى reflex

α_1-Blockers

In general, α-antagonists have been limited to selective (antagonists, which have been used to treat hypertension or to control urinary output.

α1 selective antagonist

Prazosin was the first α1 selective antagonist to be used for the treatment of hypertension

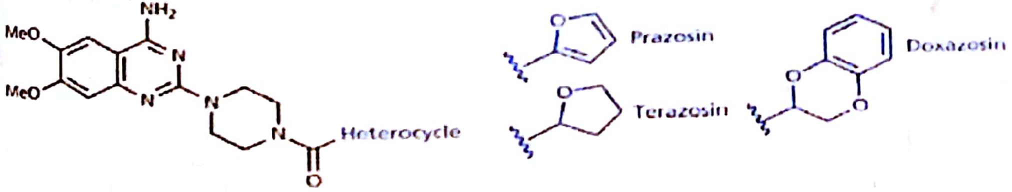


FIGURE 23.22 α_1-Selective antagonists.

α2 selective antagonist

α2 -Antagonists are being considered as antidepressants. Depression is associated with decreased release of noradrenaline and serotonin in the CNS, and antidepressants work by increasing the levels of on of both of these neurotransmitter.

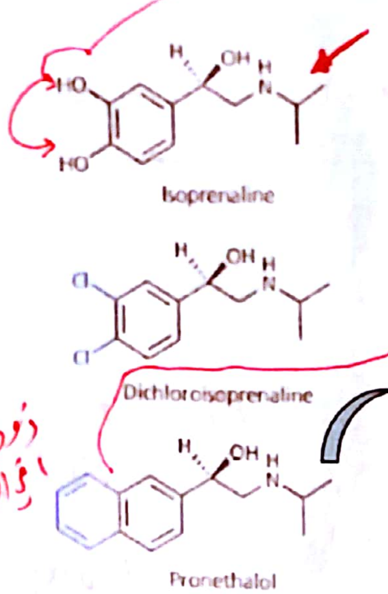
هذا الدواء B-agonist أشتق الكلية ~~B-Agon~~ B-Antigonist

β Blockers as cardiovascular drug

antiagonist

① جاء عالم أسمه بلاك قام حول 2-OH إلى 2-Cl كلورين يكبر لأن الكلور حقة السالبية الكهربائية عالية لكن منفعش ما زال الدواء B-agonist

② قام ضاف حلقة بجانب الحلقة لما اضاف حلقة أصبح الدوا partial agonist يعني الدواء لا هو pure agonist و لا pure antigonist


HO
HO
OH
H
N
Isoprenaline
Cl
Cl
Dichloroisoprenaline
Pronethalol

① ② ذو حلقة في الوسط

FIGURE 23.24 Partial β-agonists.

The product obtained (pronethalol was still a partial agonist, but was the first β -blocker to be used clinically for angina, arrhythmia, and high blood pressure.

③ بعدين قام يزود في الطول اضاف O–CH₂ size عندما كبر في الطول أصبح الدواء B-Antiagonist NonSelective الذي هوة البروبرانول ومشتقاته

إذن لتحضير مركب B-Antagonist
① ضيف حلقة ⬡ بجانب الحلقة
② ضيف O-CH₂

③

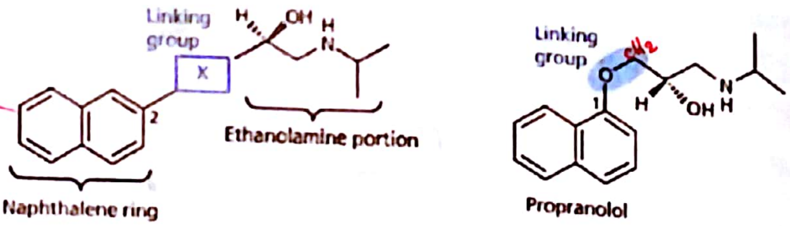

Linking group
X
2
Ethanolamine portion
Naphthalene ring
Linking group
CH₂
O
1
H
OH
N
H
Propranolol

FIGURE Chain extension tactics and the discovery of propranolol.

It was introduced into the clinic for the treatment of angina. Its contribution to medicine was so significant that its inventor James Black got the Nobel Prize in 1988. The S enantiomer is the active enantiomer although propranolol is used clinically as a racemate.

أو

ما زال مخلوط (غير مفصول)

أغلبية الأدوية التي تدخل له تكون مسطحة flat
بنفس الهرمون يدخل B

* عندما يجي للمركب فية حلقتين و ~~O-CH2~~ يكون شغال على B_1, B_2, B_3-Blockers (Antagonist) (غير Non-selective)

في حال المركب الموجود ال OH الجيدة الذي راح يعمل في hydrogen bond بدل ال O

وعندما يكون المركب فية حلقة و O-CH2 يكون شغال على B_1-Blocker selective

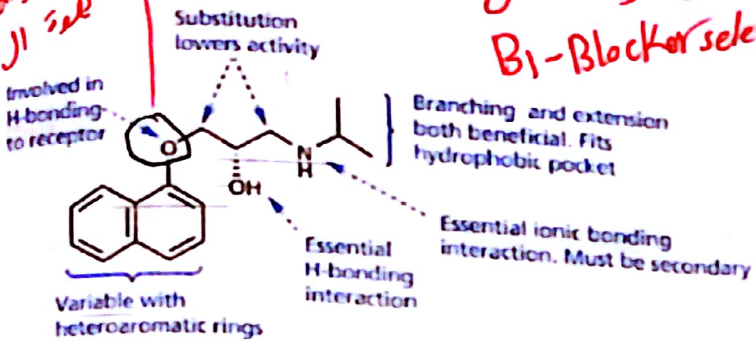

Substitution lowers activity
Involved in H-bonding to receptor
Branching and extension both beneficial. Fits hydrophobic pocket
Essential H-bonding interaction
Essential ionic bonding interaction. Must be secondary
Variable with heteroaromatic rings

FIGURE 23.26 Structure-activity relationships of aryloxypropanolamines.

~~aryl + oxy + propanolamine~~

* مستعمل B_2 Antagonist أكثر

مستعمل B_1 antagonist

β-blocker Non selective ← سمينة

B_1-blocker selective ← نحيفة

2: β adrenoceptor antagonist (β adrenergic blocking)

A: Non-selective β-adrenoceptor antagonist

B_1 / B_2 / B_3

Propranolol (Inderal®)		
Pharmacokinetics		- It has low bioavailability when given orally due to first pass effect.
تنقص الضغط B_1 في الحالة الطبيعية كانت تعمل (+)	Heart	B_1-Block - (-ve) Inotropic & (-ve) Chronotropic (HR). - (-ve) Dromotropic (Slowed AV conduction). - Decrease cardiac work and O_2 consuming → useful in angina.
في الحالة الطبيعية تعمل B.D. V.D ممكن عند فعلها V.C بتقلل تدفق الدم في كل الاعضاء (الوريد الحول)	Blood Vessels	- Blocking $β_2$ on the skeletal muscle → Block VD. - VC due to unopposed α receptor (blocking β receptor → All adrenaline and noradrenaline act on α receptor cause VC). - VC → Cold extremities and intermittent claudication. (ضعف متقطع) عرج - Decrease blood flow to all organs except the brain. (ماعدا)
ماعدا للاعضاء Pharmacological	Blood Pressure	- Prolonged (4weeks) administration → Hypotension → *due to* 1: Blocking $β_1$ of heart → Decrease CO. 2: Blocking $β_1$ of CNS → Decrease sympathetic outflow. 3: Blocking $β_1$ of Kidney → Decrease rennin release. ~~غير~~ 4: Blocking presynaptic β → Decrease NE release. 5: Resetting the sensitivity of broreceptor. 6: Increase vasodilator prostaglandins (PGI_2).

من كلية ينقص للرينين حسابك اي يتحكم القفل

action	Respiratory System	- Blockade of β_2 receptors → Bronchoconstriction harmful in patients suffering from bronchial asthma
	Eye	- Decrease aqueous humor formation → Increase IOP. - *Not effect* on pupil size or ciliary muscle or accommodation. work in smooth muscles B_2
	Metabolic effect	1: Block β_2 in Liver → ↓Glycogenolysis. 2: Block β_2 in Pancreas → Decrease insulin release. 3: Block β_2 in skeletal muscle → Hyperkalaemia. 4: Block β_1 and β_3 → decrease Lipolysis. 5: Increase triglycerides and decrease HDL.
	Q: Propranolol should be used with caution in insulin-dependent diabetics? A: It impairs recovery from hypoglycaemia since catecholamine may be the major factors in stimulating glucose release from liver in response to hypoglycaemia (i.e. it masks the symptoms of hypoglycaemia except sweating).	

	Plasma lipoproteins	- Chronic use → increase LDL (low density lipoprotein) (Bad cholesterol) and decrease HDL (high density lipoprotein) (good cholesterol) → Coronary artery disease.
	Na^+ retention	- Increase Na^+ retention → increase water in blood → increase blood volume → To avoid that → administration of diuretic to prevent Na^+ retention.
		Q: Drug interaction between Furoseinide (Diuretic) and Propranolol?
Uses الاستخدامات ١ يمنع تحويل T4 الى T3 بيوقف الزايد ال sympathetic عن طريق ال B	1: Hypertension. 2: Ischemic heart disease (Angina) → Decrease cardiac work and O_2 consuming. 3: Cardiac arrhythmia → block A-V conduction. 4: Hyperthyroidism (Thyrotoxicosis). ➔ Thyrotoxicosis (increase secretion of thyroid hormone). ➔ Types of thyroid hormone. - T_4 → thyroxine-4 - T_3 → thyroxine-3 → is more potent. ➔ Propranolol inhibits the peripheral conversion of T_4 into T_3. 5: Anxiety states to control sympathetic symptoms. 6: Symptomatic treatment of alcohol and opiate withdrawal. 7: Migraine prophylaxis due to VC effect to blood vessels in brain.	

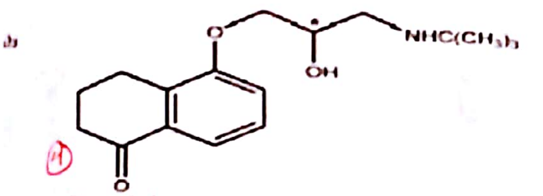
الشقيقة B2 يعمل V.D توسع زاد الصداع
نجيب B2-blocker يعمل V.C وبالتالي عالج الصداع.

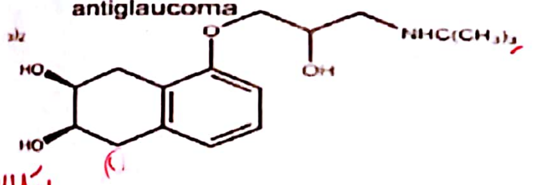
الأعراض الجانبية Adverse effects	1: Bronchoconstriction. 2: Hypotension. 3: Bradycardia and heart block. 4: Heart failure and physical fatigue due to decrease cardiac output. 5: Increase incidence of hypoglycaemic episodes in type I diabetics. 6: Cold extremities (symptoms of peripheral vascular disease) due to all adrenaline and nor-adrenaline act only in α receptors especially α_1 →VC 7: CNS effect → cross BBB → sleep disturbance. 8: Increase plasma conc. of LDL → Atherosclerosis → Angina 9: Sudden Stop β-blockers → Up-regulation of adrenoceptors → cardiac arrhythmia and hypertension (May cause sudden death). sensitive
لا يعطى لحالات Contraindication	1: Bronchial asthma. أزمة 2: Hypotension. → Bradycardia وايضا Tachycardia 3: Heart Failure (Avoid large dose) 4: Partial heart blocker.

Nadolol (Corgard®)	**Timolol** (Timogel®)
-More potent than Propranolol -Less central effect due to fewer lipids soluble. -Longer duration of action.	- More potent than Propranolol. - Used in treatment of Chronic open-angle glaucoma.
Sotalol (Betacor®)	Antiarrhythmic and Antihypertensive.

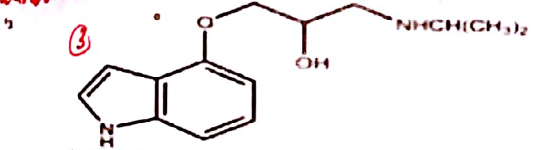
lol → always B-Blockers.

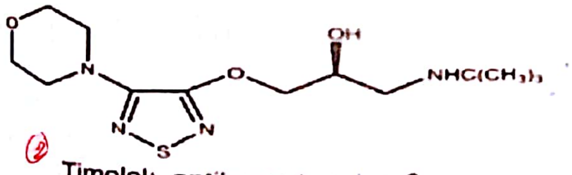
أول ما تحصل في الأخير lol lol
كلها يكون B-blocker


Bunolol
Levobunolol, S(-) isomer of bunolol
antiglaucoma


Nadolol: antihypertensive

اقل ايضا
Long duration


Pindolol: antihypertensive


Timolol: antihypertensive & antiglaucoma

كلهم نفس الآلية فقط الاختلاف
في الجرعة هذا الـ[illegible] يتأخر
مثلا هذا الثاني يخرج اسرع

Bunolol
Nadolol
Pindolol
Propranolol

* الذي يخرج سريع هو أكثر جرعة

* الذي تركيزه 20 و 50 الثاني يخرج سريع ؟
ابو 50 يخرج بسرعة لذلك أضطر ازود
لك الجرعة من اجل أعوض.

B: Selective β_1-adrenoceptor antagonist

Metoprolol (Betaloc®)	Atenolol (Atelol®)
- Absorbed in GI. - Low bioavailability due to first-pass. - Used once daily due to extend release. - Used as Antihypertensive and anti-anginal.	- Water soluble drug → Not pass BBB - Accumulation in renal tubules→ Renal failure - More effective in combination with diuretic. - Used as Antihypertensive and anti-anginal.

B1 [illegible]

Q: Advantage of using selective β_1-adrenoceptor antagonist in treatment of hypertension than non-selective?

تنقص الضغط . برودة الأطراف

A: They can be used in hypertension patient with: Tinnens امراض الطرفية زي تنميل

1: Impaired pulmonary function. asthma
2: Peripheral vascular disease.
3: Diabetic patient receiving insulin or oral hypoglycaemic agents.

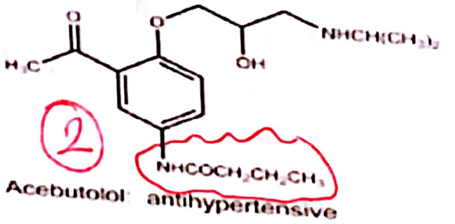
2: Arrhythmia associated with thyrotoxicosis. - **Adverse effect** :- 1: Bradycardia 2: Heart failure	Used as Antihypertensive and anti-anginal. - **Adverse effect**:- → Bradycardia, fatigue, vivid dreams and cold hands.

Betaxolol (Betoptic®) 14-22h	Bisoprolol (Concor®) 11-17h
- Long acting agent. - Used in glaucoma. high duration زرق العين	Used as Antihypertensive and anti-anginal.

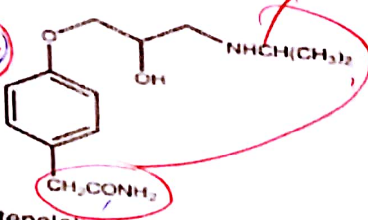
long duration [illegible]

كلهم لهم نفس الآلية فقط الاختلاف في duration عدد الكربونات

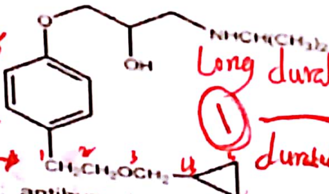
حلقة ومعاها o-CH2 أخذت الشركة الدواء الأصل و لعبت في الأطراف


(2)

Acebutolol: antihypertensive


(4) short

Atenolol: antihypertensive


أكثر فترة بيقعد في الجسم

بسبب 4 كربونات

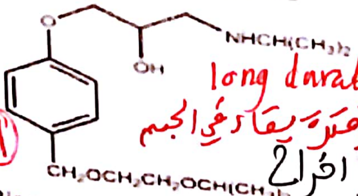
أقل افراز

less metabolism

Long duration (1)

duration أعلى (1')

Betaxolol: antihypertensive & antiglaucoma

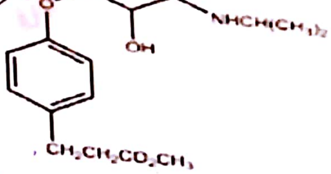

long duration

أكثر فترة بيقعد في الجسم

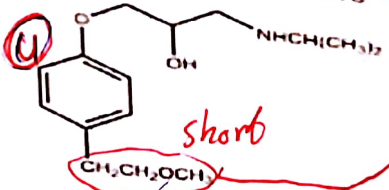
أقل افراز

less metabolism

Bisoprolol: antihypertensive


(3)

Esmolol: short-acting antihypertensive


(4) short

أقل فترة بيقعد في الجسم

less duration

fast metabolism

Metoprolol: antihypertensive

كل مدة الأدوية تقلل blood supply وبالتالي تقلل الجنس عشان كدا ال metoprolol اسموه و تحدي تنقيص الجنس Bisoprolol و Atenolol و [illegible]

Function

Sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary in nature rather than antagonistic.

Receptors

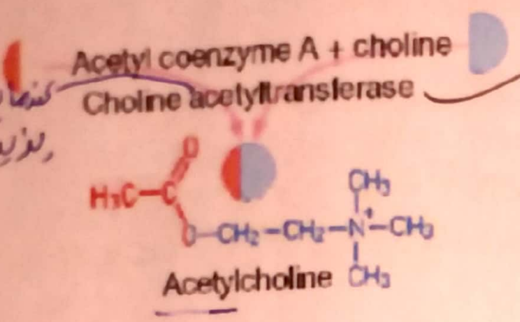
- The parasympathetic nervous system uses only acetylcholine (ACh) as its neurotransmitter.
- The ACh acts on two types of receptors, the muscarinic and nicotinic cholinergic receptors.
- Most transmissions occur in two stages: When stimulated, the preganglionic nerve releases ACh at the ganglion, which acts on nicotinic receptors of the postganglionic nerve.
- The postganglionic nerve then releases ACh to stimulate the muscarinic receptors of the target organ.

stimulate $\xrightarrow{\text{preganglionic}}$ Nerve releases Ach at ganglionc $\xrightarrow{\text{which adbson}}$ Nicotinic receptor of postganglionic

Parasympathetic (muscarinic)

- cardiac output M2: decreases
- SA node: heart rate ((−) chronotropic) M2: decreases
- cardiac muscle: contractility ((−) inotropic) M2: decreases (atria only)
- (−) conduction at AV node M2: decreases
- smooth muscles of bronchioles M3: contracts
- pupil of eye M3: contracts
- ciliary muscle M3: contracts
- salivary glands: secretions stimulates watery secretions
- GI tract motility M1, M3: increases
- smooth muscles of GI tract M3: contracts
- sphincters of GI tract M3: relaxes يفتح المواسير
- glands of GI tract M3: secretes

Drugs Affecting The
Cholinergic Nervous System


Acetyl coenzyme A + choline
Choline acetyltransferase
H₃C–C(=O)–O–CH₂–CH₂–N⁺(CH₃)₃
Acetylcholine

كلما يتوفر جزء الا تزايد
يزيد الاسيتايل كولين

يكسر
الاسيتايل

Subtypes of cholinergic receptors *

Receptor Subtype	Agonist	Antagonist	Localization
Muscarinic *G-Protein coupled receptor*	ACh Muscarine	Atropine	**M_1** ganglia **M_2** mediate acetylcholine effects on heart and vasodilating effect on endothelial smooth muscles **M_3** regulate smooth muscle tone in GIT and bronchi
Nicotinic (Nn) *Neuronal or Ganglionic*	ACh Nicotine	Trimethaphan	Postganglionic neurons
Nicotinic (Nm)	ACh Nicotine	d-Tubocurarine	Motor end plate *neuromuscular junction*

muscarinic

---

* *For more details, consult a pharmacology textbook*

Direct
indirect سوى كان

٣ أعراض [illegible]para نستخدم ال

① Glucoma
② myastheina gravis
③ post-surgical
④ Atropin-antidot
⑤ Anti-parkinsoinine

تسبب نقص الاسيتايل كولين

الاعراض الجانبية يفتح المواسير

Drugs affecting the cholinergic nervous system

1. **Cholinergic drugs**
   - a) **Directly-acting (*receptor agonists*)**
   - b) **Indirectly-acting (*cholinestrase inhibitors*)**

لتوقف الانزيم الاسيتايل كولين وبالتالي تزيد تركيز الاسيتايل كولين

لتوقف الانزيم الذي يكسر الاسيتايل

2. **Anti-cholinergic drugs**
   - a) **Anti-muscarinic drugs**
   - b) **Neuromuscular blockers**
   - c) **Ganglion blockers**

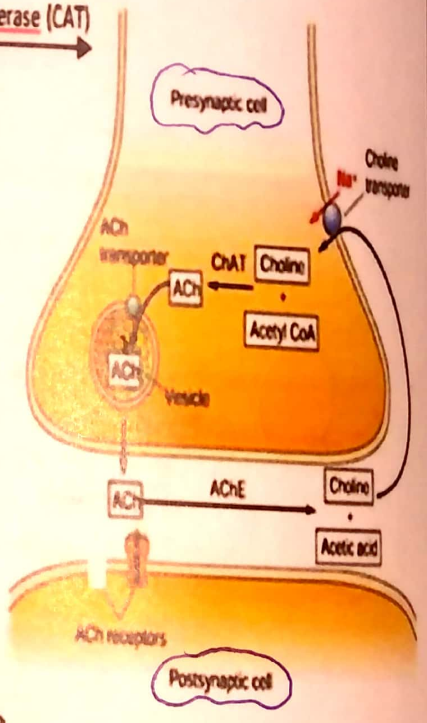
Cholinergic drugs (Parasympathetic)

A: Cholinoceptor agonist

1: Muscarinic agonist (*Parasympathomimetics*)

A: Direct-acting

- **Choline esters :-**

Formation	**Formation:** Choline + Acetyl CoA $\xrightarrow{\text{Choline Acetyl Transferase (CAT)}}$ → Ach → storage in vesicle → cholinergic receptor → response.  Presynaptic cell Choline transporter Na⁺ ACh transporter ChAT Choline ACh Acetyl CoA ACh Vesicle ACh AChE Choline Acetic acid ACh receptors Postsynaptic cell
Inactivation	**Inactivation:** ACh + Cholinesterase enzyme → Choline + Acetic acid.
Storage	**Storage:** - ACh stored in vesicle to prevent inactivation by Cholinesterase enzyme.
Choline esterase enzyme	- Enzyme which inactivate ACh - Two types :1: True (Acetyl) cholinesterase (All ACh sites, CNS & RBCs). 2: Pseudo (Butyryle) cholinesterase (Liver & Plasma).

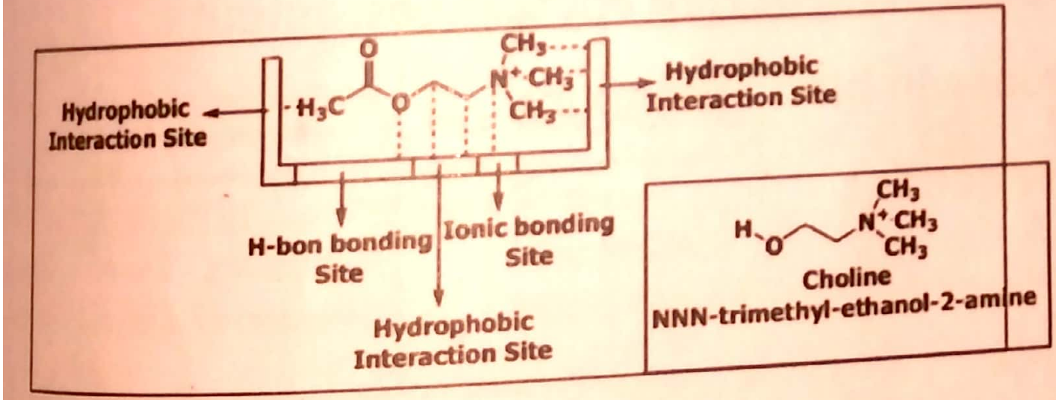
Pharmacological action	CVS	- (-ve) Inotropic, (-ve) Chronotropic & (-ve) Dromotropic → M_2
	B.V (Blood Vessels)	- M_3 receptor are stimulated with external ACh through non-innervated by NO formation → VD → Hypotension.
	GIT	- Increase secretion motility (peristalsis) → Colic pain. ✓
	U.B	- Contraction of wall and relaxation sphincter.
	Uterus	- Contraction of non-pregnant uterus.
	Bronchi ✓	- Bronchoconstriction and Increase secretion → Bronchial asthma (Difficult to breathe).
	Eye	Contraction of circular muscle → Miosis Contraction of ciliary muscle → accommodation for near vision

"مجازاً"

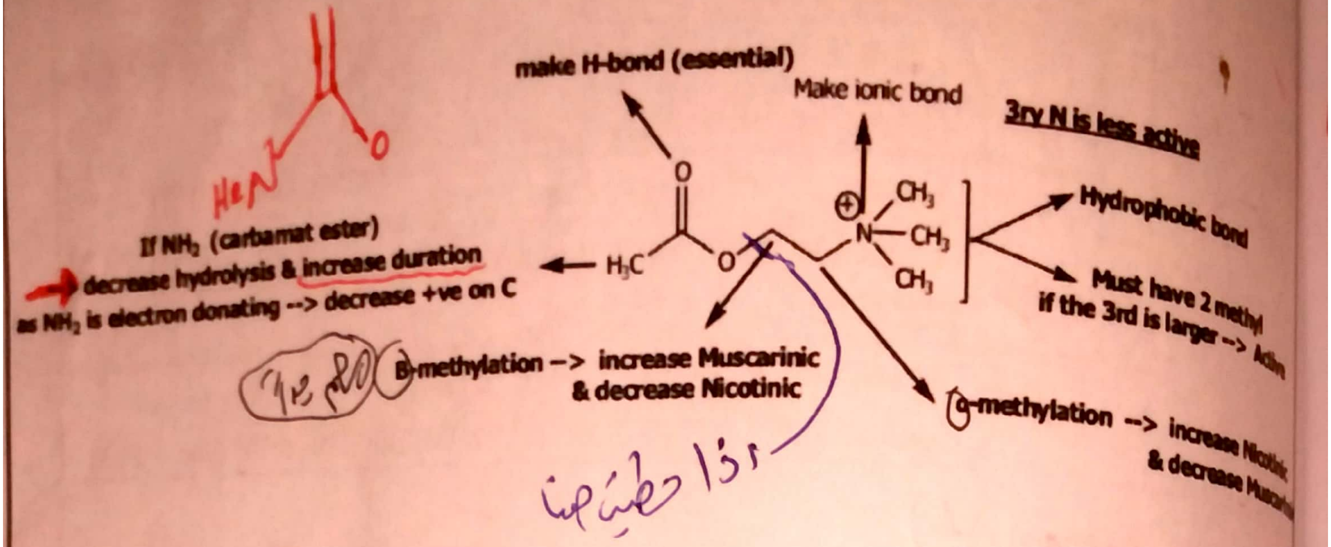
(Antigonist)

① الparasympathomimetic يشتغل كأنة sympatholytic

② والparasympatholytic // /// sympathomimetics


Hydrophobic Interaction Site
O
H_3C
O
CH_3
N^+
CH_3
CH_3
Hydrophobic Interaction Site
H-bon bonding Site
Ionic bonding Site
Hydrophobic Interaction Site
H
O
N^+
CH_3
CH_3
CH_3

Choline
NNN-trimethyl-ethanol-2-amine



H_2N

make H-bond (essential)

Make ionic bond

3ry N is less active

Hydrophobic bond

Must have 2 methyl if the 3rd is larger --> Activ

If NH_2 (carbamat ester)

decrease hydrolysis & increase duration

as NH_2 is electron donating --> decrease +ve on C

[illegible] B-methylation --> increase Muscarinic & decrease Nicotinic

α-methylation --> increase Nicotinic & decrease Muscarin

اذا حطينا [illegible]

Acetylcholine

1. Decrease in heart rate and cardiac output
2. Decrease in blood pressure
3. Other actions

لا يمتص بواسطة الفم لأنه

Acetylcholine is a poor therapeutic agent

1. Rapid hydrolysis of acetylcholine aqueous solutions particularly by acids and alkalis (poor oral bioavailability).
2. Ionic properties make it water soluble but poorly absorbed across membrane
3. In blood, it is liable to hydrolysis by esterase
4. Acetylcholine is pharmacologically non-selective as it affects both nicotinic and muscarinic receptors

- It may be used to **produce miosis** in ocular surgeries by reconstitution immediately before direct instillation into the anterior chamber.

Direct بدون حلقة الدواء

indirect وجود حلقة الدواء

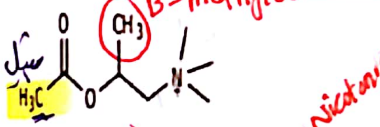
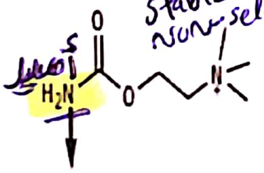
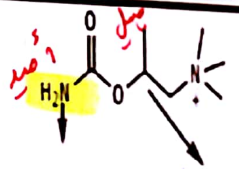
Acetylcholine.

تشبه حاجة زي اللي حلقة رب العالمين

a.Direct –acting cholinomametic

M>N

carbamate instead of ester.

Methacholine	Carbachol	Bethanechol
 B-methyl --> increase M effect & decrease N effect --> decrease hydrolysis with estrase	 decrease hydrolysis but not selective	 decrease hydrolysis --> oral active increase M & decrease N
Used as racemic mixture for glaucoma Because S is 3 times less hydrolyzed than Ach & R is competitive inhibitor of Ach.	- Uses: Glaucoma Urine retention Intestinal atony.	- Uses: post surgical urine retention & intestinal atony

B-methylation

Nicotinic

optically Inactive

stable Non-selective

Bethanechol → stable

M>N

تراخي

All of the direct-acting cholinergic drugs have longer durations of action than acetylcholine.

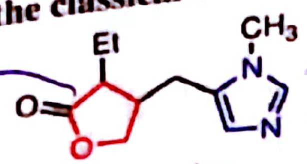
اذا قفلت الأستر يصبح لاكتون
ولو قفلت الأميد يصبح لاكتام

a. Direct-acting Cholinomimetics

ii. Alkaloids

- **Pilocarpine is the classical example**

استر حلقي ، أقل استقرار



أكثر استقرار
أميد

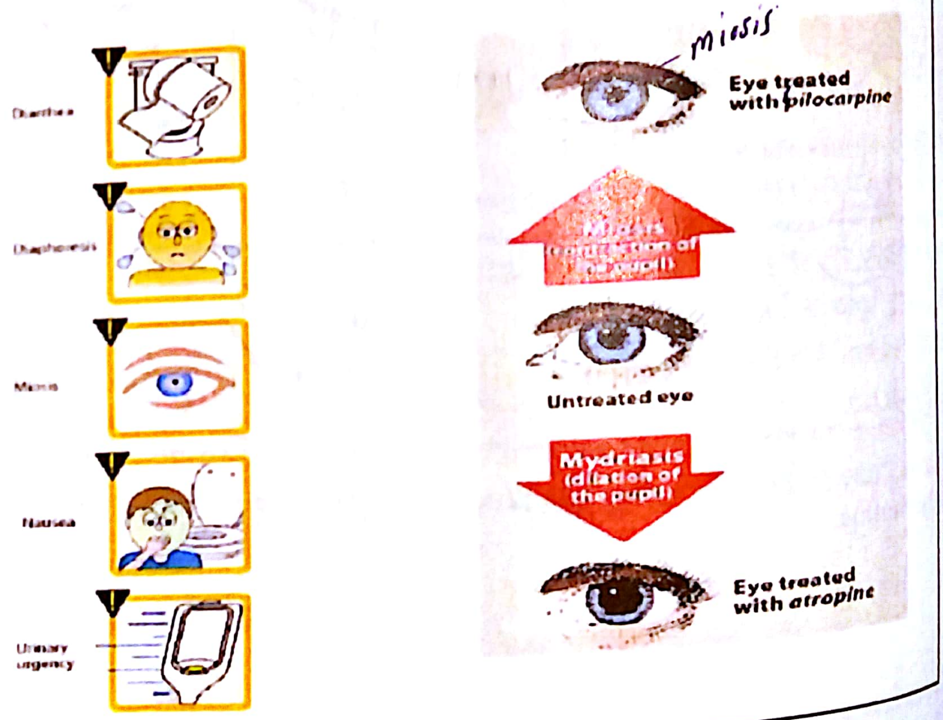
pilocarpine
3-ethyl-4-((1-methyl-1*H*-imidazol-5-yl)methyl)-dihydrofuran-2(3*H*)-one

استقرار
لو عطي بعد فترة يا السولوشن لأن اللاكتون بتتكسر

- **Chiefly used in eye drops to lower intraocular pressure in chronic simple glaucoma** *(due to its miotic effect)*
- **Stability of pilocarpine**
  - o Opening of lactone to ***pilocarpic acid***
  - o Epimerization at C3 to ***epipilocarpine***
  - o Thus the gel and/or solution should not be used 2 weeks after dispensing (open) and kept refrigerated (بالثلاجة).

Some of the more therapeutically useful drugs (pilocarpine and bethanechol) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents

Some adverse effects observed with cholinergic drugs.


Diarrhea
Diaphoresis
Miosis
Nausea
Urinary urgency
miosis
Eye treated with pilocarpine
Miosis (contraction of the pupil)
Untreated eye
Mydriasis (dilation of the pupil)
Eye treated with atropine

متصل لتوقيف للesterase وبالتالي يرتفع الاسيتايل كولين ↑

b.Anti-choline esterase: Indirect acting

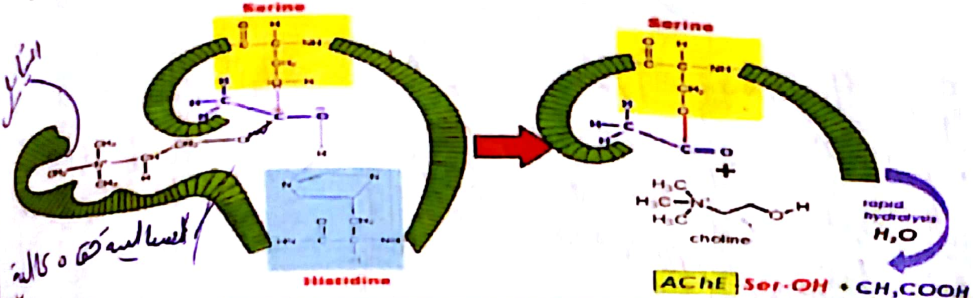
Anticholinesterases (Reversible)

- **Acetylcholinesterase** is an enzyme that specifically cleaves **acetylcholine to acetate and choline** and, thus, terminates its actions.
- **Inhibitors of acetylcholinesterase** indirectly provide a cholinergic action **by prolonging the lifetime of acetylcholine** produced endogenously at the cholinergic nerve endings. This results in the **accumulation of acetylcholine** in the synaptic space.

b. Indirect-acting Cholinomimetics

Cholinesterase Inhibitors (Anticholinestrases)

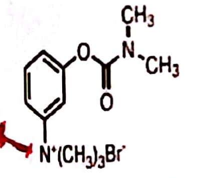
- *Mechanism of enzymatic cleavage of ACh*


Serine
Serine
Histidine
choline
rapid hydrolysis
H_2O
ACh E Ser-OH + CH_3COOH
الاستيل
السالبية ه كاملة

indirect

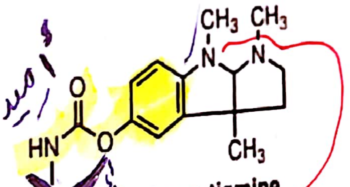
Reversible AChE-inhibitors

- Therapeutic Uses
  1. o myasthenia gravis الوهن العضلي
  2. o to stimulate the bowels and bladder after surgical لأي دواء يوقف الpara
  3. o antidote to competitive neuromuscular blocking agents
- They act by carbamylating the serine moiety at the active site of AChE (Ser-OH → Ser-O-CONR$_2$)
- Examples


CH_3
O
N
CH_3
O
$N^+(CH_3)_3Br^-$
CNS

neostigmine bromide

orally active
does not cross BBB

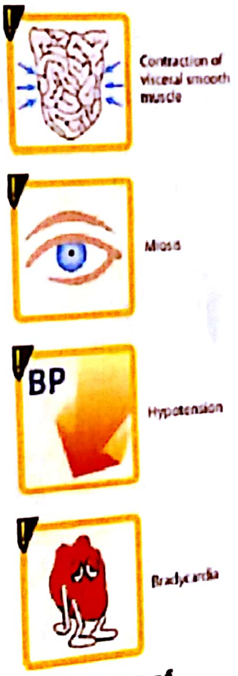

CH_3 CH_3
N
N
O
HN
O
CH_3
أميد
استر

physostigmine

tertiary amine
shows CNS side effects
improves cognitive function in Alzheimer-type dementia

carbamyl لوجود [illegible] يعتبر الدواء indirect

استر + أميد + حلقة indirect


Contraction of visceral smooth muscle
Miosis
BP
Hypotension
Bradycardia

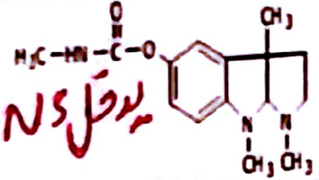
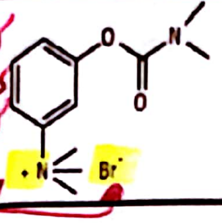
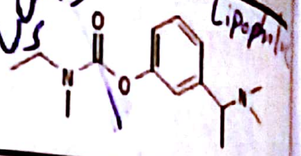
Some actions of physostigmine

الزهيمر هو نقص في المستقبلات حق الاسيتايل كولين

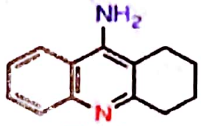
Reversible

carbamyl

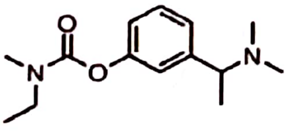
a. Aryl carbamate (enzyme substrate)

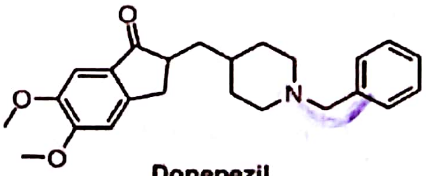
Physostigmine	Neostigmine	Rivastigmine
 CNS يدخل	 لا يدخل CNS لانه مشحون	 يدخل CNS Lipophil
Uses: - Alzeheimer (non-polar) - Glaucoma - atropine toxicity	**Uses** **Myasthenia gravis** → **polar** [NOT in alzheimer]	**Uses** : **Alzeheimer** (brain selective) → non-polar
* يمكن يعالج الزهيمر لانه يوقف انزيم الاستريز الذي يكسر الاستايل كولين وبالتالي يزيد الاستايل كولين في CNS فممكن يعالج الزهيمر.	يعالج كل شي ما عدا الزهيمر لانه مشحون وبالتالي لا يستطيع الوصول الى CNS	غير مشحون وبالتالي يعالج الزهيمر

AChE inhibitors and Alzheimer Disease


Tacrine

- **Tacrine was reported for the relief of Alzheimer disease but this advantage was outweighed by its hepatotoxicity**
- **Currently two drugs are marketed for use in Alzheimer's disease,**
  - **Donepezil** is considered AChE inhibitor, more selective to central AChE rather than peripheral one.
  - **Rivastigmine** is considered '*pseudo-irreversible*' since inhibition lasts several hours


Rivastigmine
Exelon ®


Donepezil
Aricept ®

يدخل الجسم كأنه دواء لا لا يروح يتفاعل مع الإنزيمات ويوقف عملها.

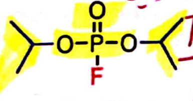
Irreversible AChE-inhibitors

في سموم القات

- They are organophosphate compounds having the capacity to bind covalently to acetylcholinesterase.

سموم القات ترتبط covalent

- Example



Isoflurophate

مرهم عين يعالج الـ glaucoma

- **Therapeutic Use :**
  - ophthalmic ointment is used topically for the chronic treatment of open-angle glaucoma.
  - The effects may last for up to one week after a single administration.

* كثر التعرض أو الشم لـ organophosphates يقوم بوقف عمل أستايل كولين استريز. يوقفه كأنه تخدير وسجمس كأنه تيبزوستاجمين يوقفه بتراكيز عالية كأنه Toxic dose

← يحصل عند المريض يرتفع الـ para أي يزيد الأستايل كولين.

← الشخص المتعرض للشم لهذه السموم يحصل عنده:
① زيادة افراز اللعاب
② miosis
③ تقل ضربات القلب
④ يقل الضغط.

← وبالتالي يدخل المريض في غيبوبة. coma

لذلك نعالج الشخص هذا بـ para-antigonist ← زي الأتروبين أو سكوبان
Atropin Hyocine

أي حاجة تكون para-antigonist تستطيع ان تنقذ المريض.

antigonist ← يروح يمنع الأستايل كولين من الارتباط أي تخفف من الـ over dose على الرغم ان سموم القات ترتبط covalent فعندما نعطي antigonist يحاول يسبق الى الاعضاء التي لم يوصل إليها السم فتمنعه من الارتباط.

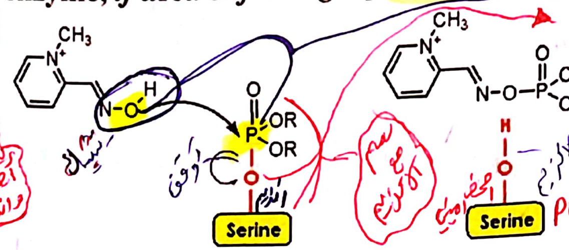
Treatment of Organophosphate toxicity:

Antidote for AChE-inhibitors toxicity

- **Pralidoxime** (PAM), can regenerate the enzyme, *if used before aging* **(6-8hrs)**

→ Antidote for organophophate.

حقنة تعالج الإنزيم الذي تثبط بواسطة السموم



فى الامكان complete أصبح التركيب ثابت وانتهى الشئ

الفوسفات مرتبطة مع الانزيم تقوم الـ antidote بسحب حق ترتبط مع الفوسفات حق الانزيم وبالتالي يرجع يشتغل الانزيم من جديد.

* السيرين معه H-O السم لما أجى ارتبط مع الـ O أصبح الانزيم متوقف والأستايل كولين ارتفع ← نجيب pralidoxime معه O pralidoxime من التركيز العالي حق يقوم بكسر الفوسفات من داخل الانزيم ويرتبط مع الفوسفات ويعود ويشتغل الانزيم من جديد أي يرجع يكسر الأستايل كولين من جديد فيعالج الشخص

- **Atropine** is used in emergency to **reverse** signs of **AChE inhibitors intoxication** *(doses up to 100mg/day, preferably divided as atropine is toxic itself)*

* الأستايل كولين استريز مهم في حياتنا لأنه إذا توقف راح يزيد الأستايل كولين وبالتالي راح يتفوق على السيمباثاوي أي بتشوف ان السمبثاوي معاد يشتغل لان الـ para زاد

para > symp ← اذا زاد هبوط في الضغط هبوط في ضربات القلب

الاتروبين في الجرعات العالية يرفع الضغط. يعمل كأنه سمباوي

a. Muscarinic Antagonists (Parasympatholyitcs)

- **Their action is competitive** (depends on their concentration and relative affinity to receptor)
- **Actions and Uses**
  - GIT
    - Decrease GIT motility → antispasmodic
    - Relief of biliary colic مغص
  - Urinary Tract
    - Antispasmodic in renal colic
    - Treatment of urinary incontinence and nocturnal enuresis in children
  - Bronchi
    - Bronchodilators in bronchial asthma
  - Eye
    - Mydriasis, contra-indicated in glaucoma
    - Loss of light reflex
    - Cycloplegia and loss of accommodation for near vision, useful in fundal examination → فحص قاع العين
  - CVS
    - Increase heart rate
    - Increase conduction at AVN so used in heart block
  - CNS
    - Stimulation of respiratory centre
    - Restlessness, hallucination and delirium
    - Anti-emetic *(inhibition of CTZ)*
    - Anti-parkinsonian effects
  - Antidote for organophosphorus intoxication

لعلاج عدم قدرة تحمل البول

enuresis التبول الليالي

في الكتب / في الواقع X → B2 agonists تخصص ←

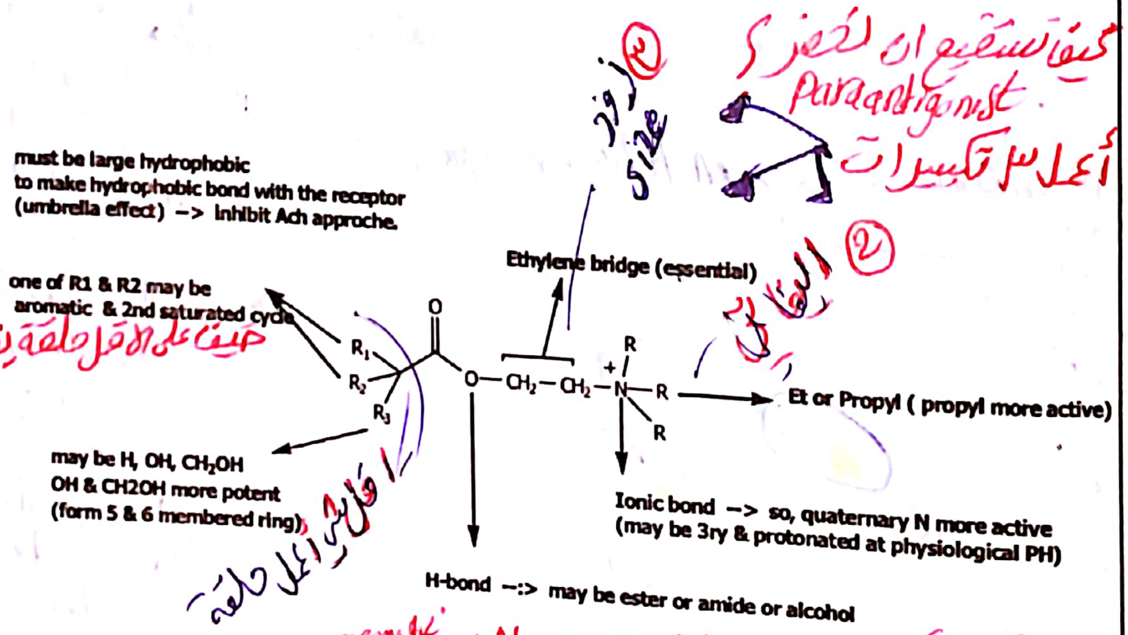
لا يوجد دواء para في السوق يعمل BD هو في الأصل تعكس السمباوي

↑AchE ↓dopamin

استخدامه في القلب قليلة لان المتحكم في القلب اصلا السمباوي ← لكن ممكن تجيب الاتروبين مع الادرينالين يرفع

[redacted]

parasympatholytic Para-Antigonist كأنه يشبه بال action Sympathomimetic



must be large hydrophobic to make hydrophobic bond with the receptor (umbrella effect) –> inhibit Ach approche.
one of R1 & R2 may be aromatic & 2nd saturated cycle
may be H, OH, CH2OH OH & CH2OH more potent (form 5 & 6 membered ring)
Ethylene bridge (essential)
Et or Propyl (propyl more active)
Ionic bond –> so, quaternary N more active (may be 3ry & protonated at physiological PH)
H-bond –:> may be ester or amide or alcohol
O
R1
R2
R3
O
CH2
CH2
N+
R
R
R

كيف تستطيع ان تحضر Paraantigonist. أعمل ٣ تكسيرات

① ضيف على الأقل حلقة بنزين

أقل شيء أعمل حلقة

② الألكائل

③ زود size

① أعمل تكسير بواسطة حلقة بنزين aromatic

② أعمل تكسير ضيف مجموعات الألكائلة بجانب الN

③ أعمل تكسير للsize مابين الاليفاتي والاروماتي.

parasympatholytics

III. Anti-Cholinergic

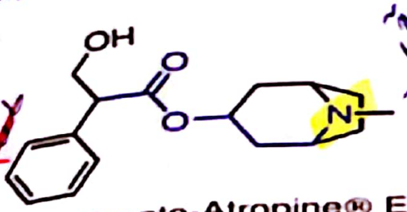
1. Muscarinic Antagonist

Action:

① Anti-spasmotic (relax smooth muscle of GIT & Urinary tract)
② Mydriatic (dilatation of eye pupil)
③ Decrease gland secretion (anti-ulcer & decrease sweeting)
④ Bronchodilators.

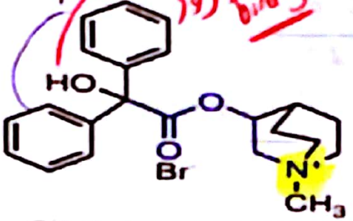
مهم

a. Muscarinic Antagonists Examples



Atropine (Isopto-Atropine® E.D.)

Prototype muscarinic antagonist
Topically used as a cycloplegic, to *temporarily paralyze the accommodation reflex,*
and as a mydriatic, *to dilate the pupils*
Antidote for organphosphate poinsoning
Treatment of heart block
Hallucinogenic, *thus controlled*



Clidinium bromide
used with
chlordiazepoxide
(tranquilizer) for
spastic colon
(Librax®)

antispasm.

antianxiety

الأدوية في السوق
أبيراكس
ليبراكس
سكلوناتا
treat IBS
irritible Bowel syndrom
انتفاخ - مغص - ضيق - قلق - إسهال
امساك في بعض الأحيان

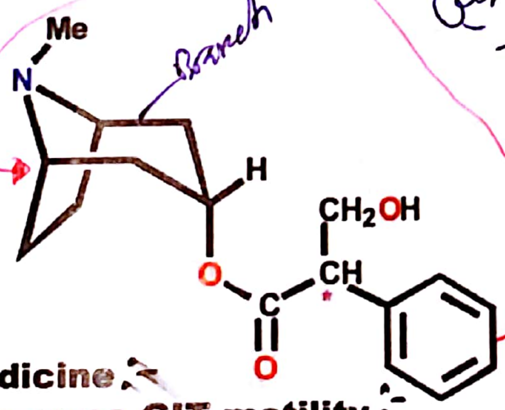
Atropin side effect
1. Dry mouth
2. Blurred vision
3. urine retention

مهم

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine

الفارق بين الأتروبين والسكوبامين
Hyocin مع ال O
يبقا الأتروبين مشوش



- Used as a medicine :-
  - → decreases GIT motility.
  - → antidote for anticholinesterase poisoning.
  - dilation of eye pupils.
- CNS side effects - hallucinations due to ↓ACh ↑Dopamine

لو زاد الأتروبين يعمل

الأعراض الجانبية Atropine

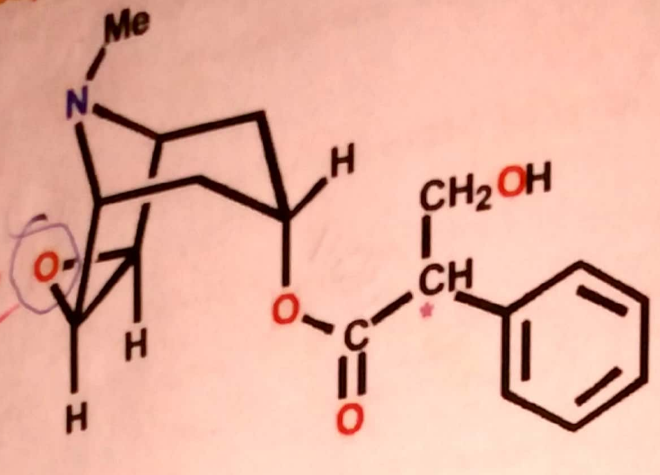
وغلولة النشفة حبست زوجها أبو سريع

Tachycardia — water retention — Dry mouth — miosis

Cholinergic Antagonists (Muscarinic receptor)

Hyoscine (scopolamine)

alti-spasmbl
can use as antidote.

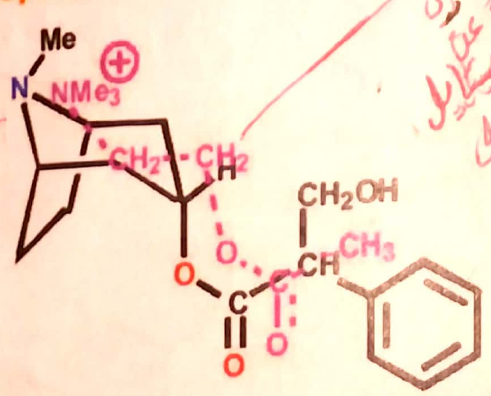


وجود اوكسجين

epoxid

Cholinergic Antagonists (Muscarinic receptor)

Comparison of atropine with acetylcholine



الينالى

المنقوط عبارة عن ذرات اسيتايل كولين أصلي كبرناه أصبح antagonist

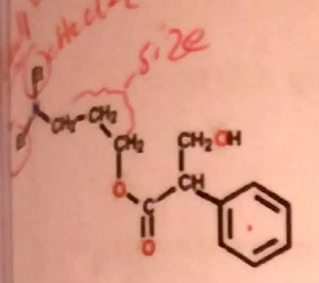
armotic ring

- Relative positions of ester and nitrogen similar in both molecules
- Amine and ester are important binding groups (ionic + H-bonds)
- Aromatic ring of atropine is an extra binding group (vdW)
- Atropine binds with a different induced fit - no activation
- Atropine binds more strongly than acetylcholine

Cholinergic Antagonists (Muscarinic receptor)

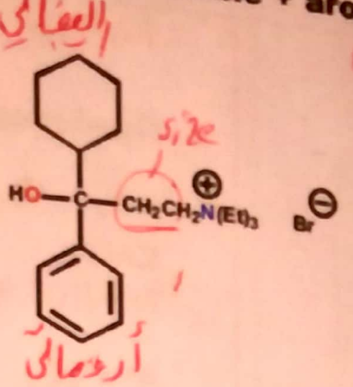
Simplified Analogues

Pharmacophore = ester + basic amine + aromatic ring ✓ ✓ ✓



Amprotropine

Antigonist



Tridihexethyl bromide

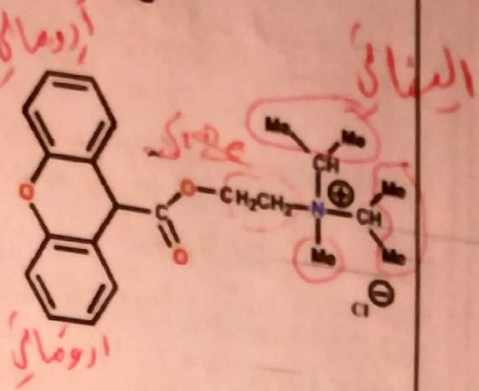
يصرف مع الامراض العصبية والنفسية

د ينقص الاستايل كولين

يعمل ارتخاء بالعضلات

relax

[redacted]

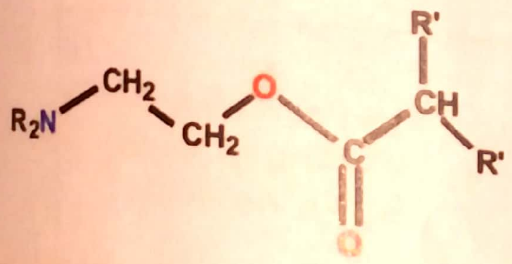


Propantheline chloride

Antigonist

12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists



R' = Aromatic or Heteroaromatic

Important features

- Tertiary amine (ionised) or a quaternary nitrogen
- Aromatic ring
- Ester
- *N*-Alkyl groups (R) can be larger than methyl (unlike agonists)
- Large branched acyl group
- R' = aromatic or heteroaromatic ring
- Branching of aromatic/heteroaromatic rings is important

12. Cholinergic Antagonists (Muscarinic receptor)

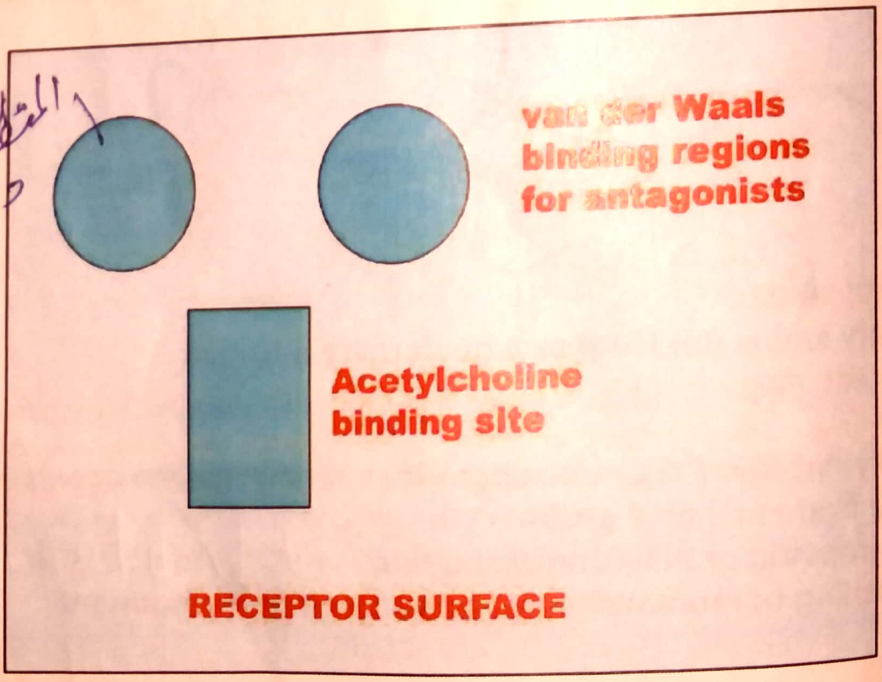
12.6 SAR for Antagonists vs. Agonists

والعكس كبير **SAR for Antagonists**	نفس الذي خلقة ربنا **SAR for Agonists**
Tertiary amine (ionised) or quaternary nitrogen	Quaternary nitrogen
Aromatic ring	
Ester	Ester
N-Alkyl groups (R) can be larger than methyl	*N*-Alkyl groups = methyl
R' = aromatic or heteroaromatic	R' = H
Branching of Ar rings important	

Cholinergic Antagonists (Muscarinic receptor)

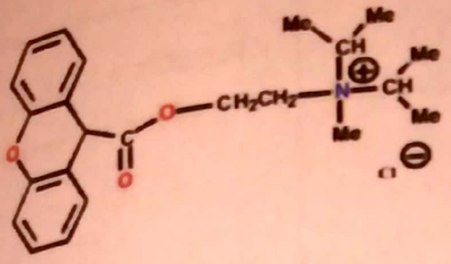
Binding Site for Antagonists

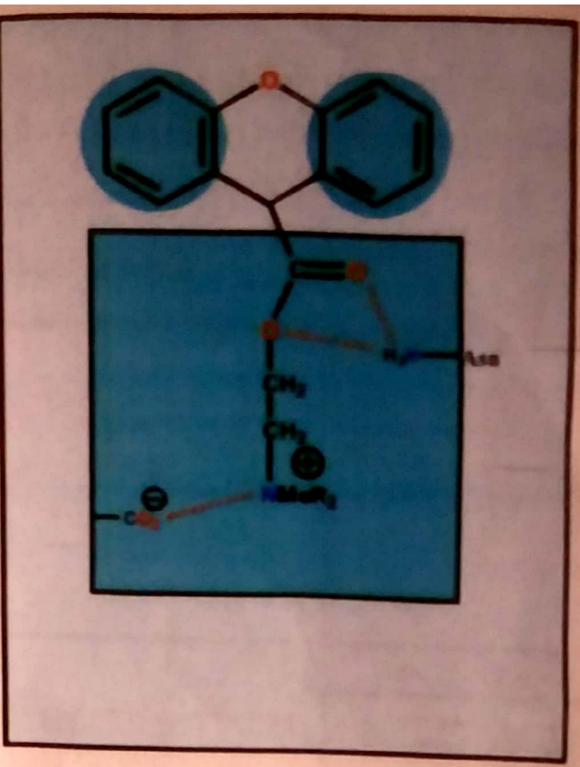
المنطقة القاطعة داخل المستقبل


van der Waals binding regions for antagonists
Acetylcholine binding site
RECEPTOR SURFACE

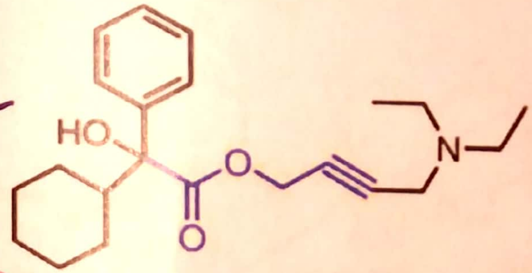
Choli

Binding Site for Antagonists


Me
Me
CH
Me
CH₂CH₂
N
CH
Me
Me
O
O
O
Cl


O
CH₂
CH₂
NMeR₂
H₂N
Asn
CO₂

a. Muscarinic Antagonists Examples



ألاعراض الجانبية له

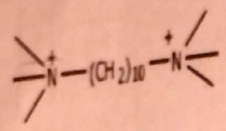
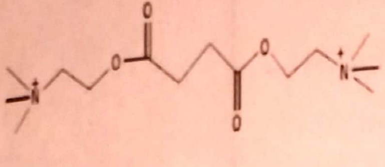
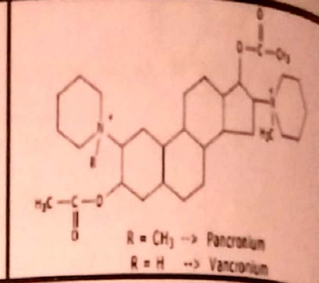
يعمل هلوسة
لأنه يقلل الاستيل
كولين ويزيد
الدوبامين

Oxybutynin (Uriban®)

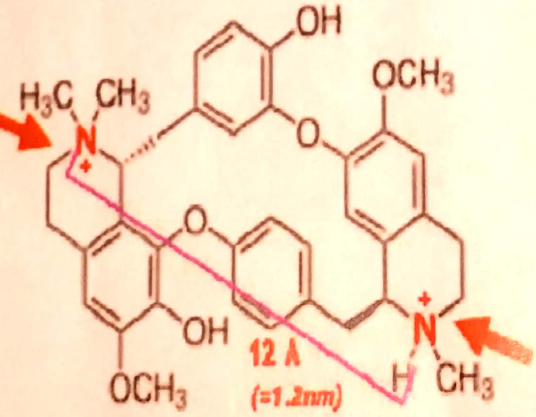
1. management of urinary frequency, urgency and urinary incontinence
2. nocturnal enuresis

Nicotinic Antagonist

- Used as **Skeletal muscle relaxant** – **aduvant to general anesthetics to ↓ dose.**
- **d-tubocurarine (parent)** → distance between 2 N^+ → 1-2 nm (one of them bind to anionic site & the other bind to nearby cysteine residue)

Decamethonium Chloride	Suxamethonium Cl	Pancronium & Vancronium
		 R = CH_3 → Pancronium R = H → Vancronium
Duration = 45 min	**Ester** → **easy hydrolysis** (5 min duration) But with side effect also	**Steroidal spacer between 2 Ach moieties** → Rapid onset & long duration = 45 min) → with no effect on B.P.
With **side effect** on the heart (↓ H.R & B.P)		

- **Prototype blocker : d-Tubocurarine *(SAR)***



binsd to a nearby cysteine residue

binds to anionic site of ACh receptor (to which Acetycholine binds)

d-Tubocurarine

compounds having 2N^+ keeping 1.2nm distance are good antagonists